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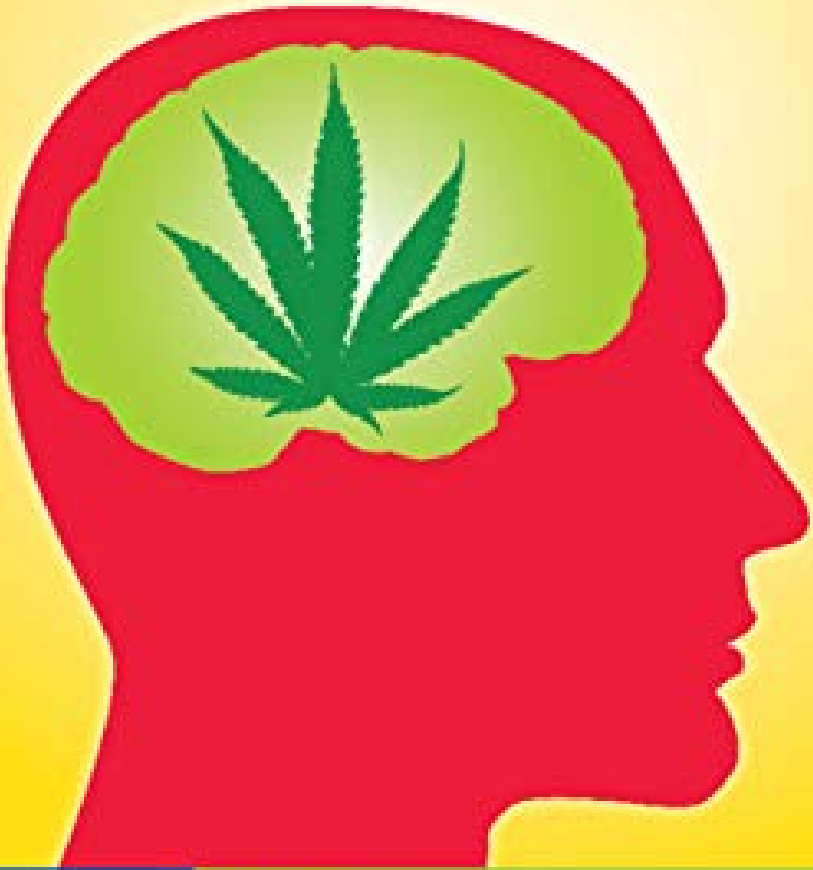
From Bud to Brain: A Psychiatrist's View of Marijuana

TIMMEN L. CERMAK



CAMBRIDGE Medicine

Foreword

From Bud to Brain: A Psychiatrist's View of Marijuana, by Timmen Cermak, represents a major contribution in the struggle to improve clinicians' and the general public's understanding of the science of marijuana and the brain's natural cannabinoid chemistry. Beginning with the assertion that the effects of marijuana cannot be understood without understanding the basic neuroscience of our endogenous cannabinoid system (ECS), Cermak reviews the fascinating history of advances in cannabis research, explaining each discovery in clear narrative language physicians, nurses, psychologists, therapists, and counselors can use with their patients. The well documented, objective, and up-to-date scientific information he reviews provides the foundation needed to understand the acute and ongoing impacts of marijuana use on the brain and mind, as well as the potential medical uses of cannabis products. While he documents the relative safety of marijuana for most adults, Cermak also focuses attention on potential risks for specific populations: adolescents, those exposed prenatally, and those at increased genetic risk of schizophrenia. Clinical vignettes, a clear explanation of motivational interviewing, and the author's personal therapeutic approach richly illustrate how science can be effectively integrated into patient education.

This book is important for two reasons. First, the process of discovering the relationships between plant and human physiology is truly an amazing story! Tracing the threads of research tying laboratories around the globe into a tapestry of competition and cooperation, exploration and discovery, makes as good reading as any detective story. Second, the book does an outstanding job of identifying the important practical implications of these research findings. The normal gap between bench and practice – between research findings and therapeutic application – has been widened in the case of cannabis to an absolute gulf by ideologic bias and misinformation. *From Bud to Brain* goes a long way to bridge this gulf.

People tend to get information about cannabis largely from personal experiences, friends, Internet websites, biased media reports, and marijuana product marketing. Unfortunately this means that the public, and even most clinicians, remain unaware of the deep body of research that is available. The author states, "This is not because the public lacks curiosity about the topic. Rather, the general lack of scientific literacy about marijuana stems from the "Googlization" of information [providing facts without context], the failure of clinicians to have objective and useful answers to patients' questions about marijuana, the superior power of stories to persuade more than facts, and scientists' difficulty translating their vast body of information about marijuana into an intriguing, easily understood narrative". *From Bud to Brain* is what we have needed to provide access to the fascinating topic of marijuana, the brain, and the mind.

The scientific research on cannabis has been robust and continuous since the 1960s. The psychoactive cannabinoid of *Cannabis sativa* and *indica*, delta-9-tetrahydrocannabinol (THC), was first isolated and described by Dr. Raphael Mechoulam in 1964. Following this seminal discovery, the human type 1 cannabinoid receptor (CB1R) was identified, isolated, and cloned. Other components of the ECS were soon identified, including two endogenous cannabinoids, anandamide (AEA) and 2-arachidonoylglycerol (2-AG), as well

as the type 2 cannabinoid receptor (CB2R) and specific enzymes that synthesize and degrade the endogenous cannabinoids. An entire neurotransmitter system exists based on chemistry similar to that found in marijuana.

Over 100 cannabinoid molecules have been identified in the cannabis plant. Three well studied cannabinoid molecules are CBG (cannabigerol – the plant's precursor for both of the more well-known cannabinoids), THC (delta-9-tetrahydrocannabinol – marijuana's most psychoactive cannabinoid), and CBD (cannabidiol). None of these plant-based cannabinoids – CBG, THC, or CBD – naturally occur in the human body. They should more aptly be referred to as phytocannabinoids (plant-based) to be distinguished from the unique "cannabinoid" molecules found in the ECS. Although not natural to the brain, phytocannabinoids can interact and affect human biology through the ECS by mimicking anandamide and 2-AG.

From the momentum of basic cannabis research came preclinical and clinical data to study the efficacy of cannabinoid-based medicines in the treatment of pain, anxiety, addiction, metabolic disorders, and a host of other health conditions. Preclinical and clinical data also documented potential harms associated with cannabis use, in particular the long-term use of THC. It is in this area, perhaps the least understood, that Cermak's book comprehensively and compellingly reviews the science of marijuana and the brain.

Exactly how THC impacts the brain to produce marijuana's characteristic "high" and what parts of the brain are impacted remained a mystery for nearly two decades after its structure was known. As scientific research unraveled this mystery, many important questions began being answered. Are there impacts that last longer than the period of acute intoxication, or that accumulate over time? How does marijuana use, especially heavy or early onset use, affect behavior, cognition, emotions, and personality? Can marijuana be addictive? And how does marijuana benefit a seemingly unconnected variety of illnesses?

From Bud to Brain is a clearly and engagingly written resource with a focus on helping clinicians and educators engage a variety of patients, from recreational users to heavy users, adolescents, worried parents, and those interested in marijuana's potential medical benefits, in meaningful conversation. Dr Cermak's extensive clinical experience caring for patients with cannabis-related concerns, his knowledge of scientific research, and his numerous publications on marijuana policy reform make him the perfect individual to advance a comprehensive, evidence-based perspective on marijuana with pragmatic value for clinicians. His work makes a very timely contribution as rapidly changing marijuana policies around the globe desperately need guidance and data-informed direction. I believe it will be a trusted resource for anyone seeking an increased understanding of marijuana, *from bud to brain*.

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Introduction

Most people get information about marijuana from friends, the Internet, popular newscasts, and personal experience – all echo chambers filled with anecdotes, opinions, exaggerations, and a smattering of facts. This is not because the public lacks curiosity about the topic. Rather, the general lack of scientific literacy about marijuana stems from the "Googlization" of information, the failure of clinicians to have objective and useful answers to patients' questions about marijuana, the superior power of stories to persuade more than facts, and scientists' difficulty translating their vast body of information about marijuana into an intriguing, easily understood narrative. Googlization encourages people to seek specific answers to specific questions without requiring familiarity with the deeper background context. People no longer need to study a field of information in order to discover individual facts that satisfy their immediate curiosity. And, of course, Google is designed to gather and present information that comports with each individual's interests. Marijuana advocates are directed toward one set of website "facts" while opponents are presented another set of cherry picked "facts," which leads to different silos of information reinforcing already fixed perspectives.

Unfortunately, while science is the most logical arbiter of fact, far too little of the fascinating and detailed discoveries about marijuana and the brain have filtered down into the public's awareness. Research has answered many of the questions continuing to puzzle the general public but its findings often remain locked away in journal articles that are too dense and literally unavailable to help most people. At the same time, the delay of information transfer commonly seen from "bench to practice" has left most health professionals less equipped than one might hope to interpret the science for their patients. (Although many clinicians have abandoned the word "patient" in favor of the more egalitarian term "client," I still prefer "patient" because its Latin meaning of "one who suffers" is an ongoing reminder to empathize with the pain that each person brings to their clinician.) Most health professionals received little or no education about marijuana during their formal training, though more than a few have personal experience with the effects of inhaling. Only 9% of medical schools teach students anything about the medical use of marijuana.[1] Once in practice, however, nearly every health professional is confronted with questions from patients about the impact of using marijuana recreationally and/or its potential medical benefits. Despite knowing far more about heart failure or depression than their patients, professionals too often have no more information to offer about marijuana than what can be read on the Internet.

I sympathize with the demands on hard working clinicians – physicians, nurses, psychologists, psychotherapists, social workers, counselors, and educators. Much is expected of them, with too little time provided for continuing their education. At the same time, I believe the public needs to be able to rely on health professionals for objective and relevant advice about the safe and effective use of marijuana. *From Bud to Brain: A Psychiatrist's View of Marijuana* provides information that health professionals, and the general public, need to know about marijuana and outlines a science-based approach to the therapeutic technique called motivational interviewing to effectively communicate this information to a variety of patients, from adult

recreational and medicinal users to those who use marijuana excessively, adolescents, their worried parents, and political leaders. I have found that each subpopulation can usually be engaged in useful conversation about marijuana if approached empathically and provided scientific information in common language that is relevant to their individual concerns.

In a 2015 *JAMA Psychiatry* Editorial a senior investigator at the National Institute on Alcohol Abuse and Alcoholism, David Goldman, asked, "In the cannabis debate, does the science of consequences and addictive liability matter?"[2] Faced with the raucous and opinionated quality of "debate" about marijuana, it is easy to understand how he might legitimately wonder about the utility of science to help the public navigate toward rational policies and personal answers about its use. Goldman authoritatively answers that "Studies of humans and animals strongly indicate that cannabis changes the structure and function of the brain, and the propensity to cannabis addiction is heritable . . ." His authority to advance science into its proper position in the debate is not merely eminence-based. More importantly, his authority is *evidence*-based in a special way; it derives from deep familiarity with the hard-fought path taken by scientists to gather the evidence. His words embody the scientific narrative.

Section 1, The Science of Marijuana and the Brain, summarizes the vast amount of scientific information that is now available about marijuana, how it impacts the brain, and thus the mind, and the basis for its potential medical uses. More detail is provided than what most clinicians will ever share with patients because the foundation of a clinician's authority depends on the depth of her or his understanding of the scientific narrative about marijuana. With the investment of only a few hours of effort, health professionals can master the core scientific discoveries, grasp how the layered patterns of discovery by different disciplines reinforce each other, and learn how to integrate basic science into motivational interviewing's ability to engage patients. Armed with scientific facts and a framework for reducing people's attachment to anecdotes and resistance to discomforting facts, it is easier to communicate the information people need to make informed decisions about whether to use marijuana, or not, and how to determine if they are using it safely. People need this information NOW, but are not sure where to turn for reliable, objective advice. After reading *From Bud to Brain*, clinicians will have the means to guide people toward healthy choices.

The need is huge. A startling 67 million adults in the U.S. (28%) can buy recreational marijuana legally with the number likely to increase to 37% by the time of publication. And over 200 million – 62% of the U.S. population, in 33 states – have legal access to marijuana for medical purposes. The United Kingdom (UK) National Health Service was authorized to prescribe medical cannabis in November 2018 although access remains limited. Canada legalized the medical use of marijuana in 2001 and in 2018 legalized recreational marijuana for ~30 million citizens aged 18 and older, making it the second country, after Uruguay, to adopt such a nationwide policy. In Australia, 35% of the population aged 14 and older (6.9 million) have used cannabis at least once, with 10.4% (2.1 million) having used in the last 12 months.[3] Australia legalized medicinal cannabis at the federal level in 2016. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA)[4] reported in 2018 that 11.5% of the UK population between 16 and 34 years old (>16 million) used cannabis in the previous year. The need for accurate, digestible information is indeed huge.

I first became curious about how marijuana works as a result of personal experience in the late 1960s, but never expected to see its mysteries solved. Despite training in psychiatry and two years of a postdoctoral fellowship in neurophysiology at Stanford University, I was still left with nothing better to explain marijuana's power than mystical theories that amounted to little more than pixie dust. As I began practicing addiction medicine, my curiosity about how marijuana changes brain function remained unsatisfied. This was in contrast to what had happened with opiates. Scientists had begun unlocking the mystery of opium, heroin, and morphine in the mid-1960s with the discovery of opiate receptors, and then of the brain's natural opiate chemistry (endorphins) in 1975. Regarding marijuana, however, I was left listening to hundreds, and eventually thousands, of people talk about their experience with no explanation to offer for how ingesting small amounts of the cannabis plant did so much more to their mental world than ingesting parsley, sage, rosemary, or thyme. Of course, we all knew the mantra that delta-9-tetrahydrocannabinol (THC) is the primary psychoactive ingredient in marijuana. But the meaning of this fancy chemical name was opaque, since no one knew what THC actually did once it got into the brain.

Fortunately, scientists around the world were also wondering about how marijuana works and they had the right tools to unravel the puzzle. I first learned that research was gradually revealing the answers I wanted when the late Billy Martin (the Abe Lincolnesque chair of Virginia Commonwealth University School of Medicine's Department of Pharmacology and Toxicology) spoke at a California Society of Addiction Medicine conference in 1997. In a review of the previous decade's research, Martin not only provided pieces of the puzzle I lacked, but also fit them together into an overall picture. The science of marijuana had advanced much further than I had dreamed possible – much, much further. Researchers not only knew by then how marijuana worked, but they had also discovered an extensive neural system permeating the brain that uses the same basic cannabinoid chemistry found in marijuana. I have closely followed the research literature ever since and have become convinced that the brain's natural cannabinoid chemistry is one of the most important and fascinating neuroscience discoveries in the last three decades. At the same time, we have only begun to understand the role played by our endogenous cannabinoids in regulating the rest of our brain chemistry.

Understanding how marijuana creates its psychoactive effects, as well as many of its medicinal uses, requires understanding the brain's natural cannabinoid chemistry – for, as I tell patients, the magic is in the brain, not in the weed. Marijuana produces its characteristic "high" by increasing the activity of our own endogenous cannabinoid neural system. Understanding this requires a radical shift in perspective – from the bud to the brain itself. Health professions have a unique opportunity to shift people's thinking from whether marijuana is safe to what their own unique brains can tolerate. As a result of making this shift, I once heard the quarterback of a high school football team I was addressing yell out to his teammates that they had better not smoke pot the day before a game because he did not want their brains dulled when they needed to protect him from getting blindsided by a massive defender intent on slamming him to the ground. (More about this in later chapters.)

Although any understanding of marijuana must begin with understanding our brain's own internal cannabinoid system, the discovery of our natural cannabinoids began with

trying to understand marijuana. Because scientific facts are best understood by knowing how they were discovered, I begin Section 1, The Science of Marijuana and the Brain, with the fascinating story of how researchers discovered our brain's natural cannabinoid system (Chapter 1) and then explain how marijuana interacts with this extensive system to produce its characteristic high (Chapter 2) and potential side effects (Chapters 3 through 9). Section 2, The Science and Art of Healing, next explains how basic science makes sense of the potential medical benefits offered by marijuana (Chapter 10) and explores how to use science to engage people in the treatment of side effects stemming from overuse (Chapters 11 through 13). Section 3, The History and Art of Marijuana Policy, reviews the often racially tinged laws and enforcement governing marijuana in the U.S. and the current post-War on Drugs liberalization, with emphasis on legalization taking place for 40 million people in the state of California (Chapters 14 and 15). An Epilogue speculates on the future of marijuana and introduces intriguing new questions about the function served by our endocannabinoid system's direct connection to the brain's reward mechanism (Chapter 16). Throughout the book I hope to communicate my fascination with the challenges of scientific research and the thrill of discovery. Brain research, like space travel, goes boldly into one of the last frontiers to be explored. No frontier is as personal as our own brain.

Marijuana and Cannabis

The proper name for this book, if it intended to serve academics rather than working clinicians and the general public, would be *A Psychiatrist's View of Cannabis*. I chose to speak of "marijuana" instead because this emphasizes the popular parlance. While there is a gradual shift to the more generic term "cannabis," most people still ask questions about "marijuana." Readers will find multiple examples through the text of descriptions of biology (e.g., receptor sites, synapses, etc.) in plain, nontechnical language. Rather than take offense at my simplifying concepts, I invite health professionals to view these descriptions as models of the images and metaphors that have helped me communicate sophisticated scientific concepts to patients with a wide range of scientific literacy. In the end, little information is effectively communicated without curiosity on the part of the recipient and my descriptions are designed to evoke curiosity wherever possible. There is no substitute for enthusiasm on your part for awakening interest in others.

At the same time, the perceived authority of health professionals often rests, especially for regular marijuana users and adolescents, on their understanding the range of cannabis products capable of delivering psychoactive experience, nuances of differing marijuana strains and the history of marijuana. The Brazilian researcher Antonio Zuardi offers an elegant introductory description of the cannabis plant: "In the tip of secreting hairs located mainly on female-plant flowers and, in a smaller amount, in the leaves . . . there are resin glands that have a considerable amount of chemically related active compounds, called cannabinoids."[5] Marijuana is the dried buds from those strains that produce enough cannabinoid containing resin to be psychoactive when consumed by humans. Just as different trees produce the best wood for building houses or the best nuts for food, different cannabis strains produce fibers more useful for industry or flower buds better suited to be ingested for recreation and medication. Marijuana should therefore be seen as only one of many products that come from different strains of the cannabis plant.

Cannabis sativa and *Cannabis indica* are the two strains that have been cultivated and carefully hybridized to produce buds with high concentrations of psychoactive compounds in order to produce the most potent marijuana possible. Other strains of cannabis have been cultivated to produce strong fibers containing virtually no mind-altering chemicals. In this way, cannabis is similar to another flowering plant – the poppy. California poppies harmlessly turn hillsides brilliant orange, while other poppies – especially those in Afghanistan – produce the raw material for opium and heroin. One variety can be bought in any nursery, but the other is illegal.

Industrial hemp comes from a variety of *Cannabis sativa* lacking psychoactive properties. Archeologists have found examples of fibers spun from hemp 10,000 years ago. Over the millennia, hemp has been used to produce a variety of commercial items including paper, textiles, clothing, biodegradable plastics, paint, insulation, biofuel, and animal feed. Hemp fiber provided ropes and canvas (derived from the word "cannabis") on ships circling the globe during centuries of exploration and migration.

My curiosity is focused only on those strains of cannabis that have been bred for high levels of biological activity. Written history since 5000 BC is replete with descriptions of marijuana's power to treat illness and "change the texture of our . . . experience,"[6] from Chinese emperors extolling its virtues to Napoleon's soldiers starting a craze in Paris after bringing marijuana and hashish (concentrated cannabis oil) back from their military campaign in Egypt circa 1800. The last 40 years have seen the largest increase in marijuana's potency in history, most often measured by its percentage of THC. Dedicated horticulturists in Amsterdam and Northern California cross-pollinated the strongest cannabis strains to produce competitively more powerful hybrids. Improved growing techniques, including hydroponics and specialized indoor lighting, have also increased potency. Sinsemilla (Spanish for "without seeds"), for example, is marijuana harvested from female plants grown isolated from male plants. Males are only useful for pollinating females to produce seeds. They contribute none of the effects of marijuana that people commonly seek because male plants contain few of the psychoactive chemicals found in the flower buds produced by females. The highest THC marijuana at the 2015 Cannabis Cup in Denver, named "Emperor Cookie Dough," averaged 29% THC. Hashish is the resin concentrated from marijuana and contains up to 65% THC, while newer forms of extracting and solidifying marijuana's essential oils, variously called dabs, shatter, wax, and budder, produce concentrations of THC up to 90%. These new methods, which can easily be found on the Internet, use dangerous volatile chemicals such as butane in the extraction process. Serious explosions have occurred.

People often refer to today's more potent marijuana as a "different" drug than the 3% THC pot of the 1960s. The "difference" is only a matter of greater concentration of the same drug, similar to the difference between beer and hard liquor. The alcohol molecule is the same in both, but tequila will get you drunker, and faster, than Budweiser because it contains a higher concentration of alcohol molecules. Similarly, the cannabinoid molecules in Emperor Cookie Dough are exactly the same as in earlier, weaker marijuana. Unlike alcoholic beverages, however, marijuana contains far more than just one chemical. Over 100 cannabinoid molecules have been identified in marijuana, as well as nonpsychoactive volatile hydrocarbon oils called terpenes that give marijuana its characteristic smell. (Terpenes unique to the oil from pine trees is distilled into turpentine.)

Three cannabinoid molecules that have been well studied are cannabigerol (CBG) – the plant's precursor for both of the next two more well known cannabinoids, delta-9-tetrahydrocannabinol (THC) – marijuana's most psychoactive cannabinoid, and cannabidiol (CBD) – possessing only mild psychoactive properties and very complex, still only partially understood modes of action. None of these plant-based cannabinoids – CBG, THC, or CBD – naturally occur in the human body. They should more properly be referred to as phytocannabinoids (plant-based) to be distinguished from the unique "cannabinoid" molecules described in the next chapter that are produced in animals. The ability of some phytocannabinoids to interact with human physiology is probably a coincidence. The phytocannabinoids in marijuana evolved for the cannabis plant's unique, and still to be determined survival needs. On the other hand, as Michael Pollan details in *Botany of Desire*, the attraction marijuana has for some people has led to the cannabis plant's sudden evolutionary boost in production of its essential oils, similar to how the Dutch infatuation for tulips in the early 1600s led to a sudden increase in varieties of color.

The simple fact is that THC, the other phytocannabinoids, and terpene molecules are foreign to the human body. That does not, in and of itself, make the molecules bad or destructive. But it did create the central mystery of how THC interacts with our brain – a mystery that persisted for nearly two decades after the structure of THC was known. *Exactly* how does THC impact our brain to produce the experience of being high? And what part of the brain is impacted? Beyond this, other questions abound. Are there impacts that last longer than the period of acute intoxication, or accumulate over time? How does marijuana use, especially heavy or early onset use, affect our behavior, cognition, emotions, and personality? And how does marijuana benefit a seemingly unconnected variety of illnesses? None of these fascinating questions will ever be answered by studying only the botany of cannabis or the chemistry of marijuana. The answers lie within the realm of neuroscience.

The expanding availability of legal marijuana (and the rapid shift toward high THC extracts) for both recreational and medicinal use increases the public's need to be well informed about how this plant affects the brain. Nothing illustrates confusion about marijuana more than the fact that, while the U.S. Food and Drug Administration (FDA) classifies marijuana along with heroin and LSD as a Schedule I drug having high abuse potential, no medical use, and severe safety concerns while approving pharmaceutical preparations of both THC and CBD, and while a recent Attorney General strongly opposed all marijuana use because "Good people do not use marijuana,"[7] at the same time Congress prohibits the Justice Department from spending funds to interfere with the implementation of state medical marijuana laws.[8] It is clearly time to bring a better understanding of the neuroscience underlying marijuana's power into the town square of public discussion. Physicians, psychologists, nurses, psychotherapists, and counselors can play a major role in educating the public by bringing the latest science of marijuana into their medical and mental health practices. Preparing to fill this role begins with learning not only the scientific facts about marijuana but also how these basic facts were established. The next chapter tells the story of how marijuana researchers discovered our natural cannabinoid neural system.

Clinical vignettes appearing at the end of chapters are composite sketches of patients I have treated, with names changed and all identifying information deleted.

The intent is to illustrate how I have learned to integrate evidence-based scientific information into a motivational interviewing approach. These vignettes are set apart from the main text in order to permit readers to focus on, or skip over, them as fits individual interests.

Notes

1. A. B. Evanoff, et al. Physicians-in-training Are Not Prepared to Prescribe Medical Marijuana. *Drug and Alcohol Dependence*, 2017; **180**: 151–5. (Published online September 4, 2017.)
2. D. Goldman. America's Cannabis Experiment. *JAMA Psychiatry*, 2015; **72**(10): 969–70.
3. Australian Institute of Health and Welfare 2017. National Drug Strategy Household Survey 2016: detailed findings. Drug Statistics series no. 31. Cat. no. PHE 214, Canberra, AIHW. p 61. www.aihw.gov.au/reports/illicit-use-of-drugs/ndshs-2016-detailed/contents/table-of-contents. (Accessed March 14, 2019.)
4. Country Drug Report 2018: UK. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), Praça Europa 1, Cais do Sodré, 1249–289 Lisbon, Portugal. www.emcdda.europa.eu/countries/drug-reports/2018/united-kingdom/drug-use_en. (Accessed March 14, 2019.)
5. A. W. Zuardi. Cannabidiol: From an Inactive Cannabinoid to a Drug with Wide Spectrum of Action. *Braz J Psychiatry*, 2008; **30**(3): 271–80.
6. M. Pollan. *Botany of Desire*, Random House, 2001.
7. C. Ingraham. Trump's pick for attorney general: 'Good people don't smoke marijuana'. *The Washington Post*. November 14, 2016. www.washingtonpost.com/news/wonk/wp/2016/11/18/trumps-pick-for-attorney-general-good-people-dont-smoke-marijuana/?utm_term=.919f194b719d. (Accessed March 14, 2019.)
8. The Rohrabacher–Farr Amendment prohibiting the Justice Department from spending funds to interfere with the implementation of state medical cannabis has been passed annually since 2014.

Chapter

1 Monumental Marijuana Discoveries

The discovery of cannabinoid chemistry began with Raphael Mechoulam, born in Sofia, Bulgaria in 1930. Anti-Semitism stripped Mechoulam's father of his hospital leadership and sent him to a lesser position outside Sofia, and then to a Nazi concentration camp. After his surviving the camp, the family immigrated to Israel in 1949 when persecution continued after World War II under communist rule.

Mechoulam's interest in chemistry led to his being assigned to an Israeli army unit researching pesticides. This experience began a lifelong pursuit of the "sweet taste of research," which he called "an addiction from which I do not want to be cured."[1]

Returning from postdoctoral studies at the Rockefeller Institute in New York in the early 1960s to a junior faculty position at the Weizmann Institute of Science in Rehovot, Israel, Mechoulam began looking for an "important topic" to begin his research career. He was especially fascinated by the interaction of chemistry and biology and saw a ripe opportunity with marijuana. While morphine had been isolated and identified as the most active compound in opium (the gummy harvest from immature poppy seed pods) 150 years before, and cocaine had been isolated from coca leaves 100 years before, the active component of marijuana was still unknown. It had not yet been isolated in pure form, its structure had not been identified, and essentially no one else was working on it at the time. Here was a mystery waiting to be solved, and a young researcher looking to make his mark was just the person to solve it.

Raphi, as colleagues often call him, still enjoys telling how his grant proposal to study marijuana was rejected by the U.S. National Institute of Health (NIH) on the grounds that, according to the NIH, "Marijuana is not an American problem." He was told to return with a request for funds when he found "something relevant" to research. One year later, Mechoulam recounts with amusement, the head of pharmacology at NIH, Dan Efron, traveled to Israel to meet with him. Apparently, a U.S. Senator had

caught his son smoking pot and called Efron to ask if it was destroying his son's brain. In Mechoulam's words, NIH knew they "didn't have the foggiest idea what marijuana does." By that time Mechoulam and his team had painstakingly isolated the active ingredient in marijuana – THC. Efron flew back to NIH with 10 grams of the purified extract in his pocket and Mechoulam received NIH funding for the next four decades without any interference in his research by our government.

Mechoulam's team published the first report of successful isolation and identification of THC with proof it was the primary psychoactive component of marijuana in 1964.[2] Two factors aided this discovery: first, the recent development of more powerful instruments for separating THC from the profusion of other chemicals in marijuana, including many that closely resemble THC, and then identifying its structure, and second, the convenience of working in a small country.

In order to isolate THC, Mechoulam needed a good supply of marijuana or hashish. Naïve about how to get enough raw material to work with, Mechoulam asked the director of the Weizmann Institute for help. A call to the director's old army buddy at police headquarters in Tel Aviv to vouch for the young professor's reliability quickly secured five kilograms (11 pounds!) of superb hashish that had been captured from Lebanese smugglers. Not having a car, Mechoulam took a bus to Tel Aviv to retrieve the hashish. By the time he completed the 17 miles back to Rehovot, fellow bus passengers were trying to figure out the strange odor coming from his bag. When he later realized he had broken the law by not first obtaining a permit from the Ministry of Health, Mechoulam apologized at the ministry in person. Many officials at the ministry were his former students and, after giving him a gentle scolding, they quickly forgave his transgression. With the ministry's written permission from that point forward, Mechoulam continued to obtain marijuana and hashish from the police for over 40 years.

Mechoulam and Yehiel Gaoni, an organic chemist, began searching for the active component in hashish by extracting its oils with a highly volatile hydrocarbon solvent. They then separated the over 400 compounds in the extract by repeatedly pouring it through a glass tube filled with aluminum oxide. Different oils ran through the tube at different speeds, which enabled researchers to separate each by collecting filtrates at different times. A colleague administered each of the different oils to rhesus monkeys and only one oil caused the same sedation known to be produced by marijuana. Ten members of Mechoulam's research team participated in a blind study with half getting the same oil as the monkeys and half getting a placebo. It was immediately apparent that those getting the active oil were affected quite differently than those getting the placebo. Some felt "weird," some felt nothing but talked or laughed a great deal, and one became visibly anxious. Those who were familiar with the effects of marijuana recognized that the oil they had extracted from hashish felt similar. At that point Mechoulam's team had isolated the active component in the cannabis plant, but what exactly was it?

The structure of this active component was determined by using the same principle as medical Magnetic Resonance Imaging (MRI) scans, which generate a strong magnetic field to analyze the resonance of hydrogen atoms to form images of structures in the body. Chemists use a mass spectrometer with a wide spectrum of magnetic frequencies to identify the different atoms in complex molecules. The active component in Mechoulam's psychoactive extract from hashish, called delta-9-tetrahydrocannabinol (THC) (Figure 1.1), had the following structure:

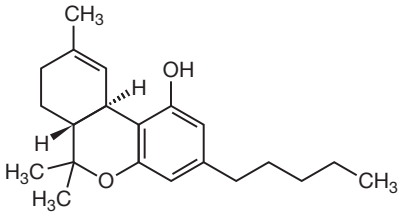

Figure 1.1 The structure of delta-9-tetrahydrocannabinol.

Discovering the structure of THC was important. Scientists could now synthesize the compound in its pure form, which was a lot easier than separating it from other molecules by the tedious chromatography process of repeatedly pouring cannabis oil through a column and catching what dripped out at precisely the same time each trial. Not only could Mechoulam now synthesize THC, but he also incidentally noted that THC's structure had much in common with a fatty acid (arachidonic acid) found in all cell membranes – an observation that became highly relevant 20 years later. Chemists around the world began modifying the basic THC molecule to form new analogs – that is, chemical compounds that are structurally similar but differ slightly in their composition. The world of synthetic cannabinoids was born in laboratories for research purposes. For example, in 1974, Pfizer Pharmaceutical created CP-55,940, a compound 45 times more potent than THC that subsequently contributed to further important cannabinoid research. Clemson's John W. Huffman developed a series of numbered compounds beginning with his initials, JWH, while Mechoulam contributed HU-210 (which is 100 times stronger than THC) – all for the purpose of furthering research into how THC affects the brain. Synthetic cannabinoids produced in laboratories and not found in the cannabis plant clearly represented new, more powerful, and potentially riskier drugs if used recreationally. Unfortunately, several synthetics have been pirated from laboratories, sprinkled on innocuous herbs such as oregano, and sold under brand names such as Spice and K2. These powerful synthetic cannabinoids can do serious harm requiring emergency medical care, including extreme anxiety, confusion, and paranoia.

The next couple of decades were busy for Raphael Mechoulam as he continued to explore the chemistry contained in cannabis plants, a new branch of research that he called "cannabinoid chemistry." He participated in multiple studies researching the potential medical benefits of marijuana's compounds, especially of CBD, the structure of which he had characterized the year before his discovery of THC.[3] But the biggest mystery was still unsolved: how did THC interact with the brain to produce its effects? There were some indications that it produced changes in cells similar to those seen with molecules for which unique receptor sites were present, but undetected impurities in THC's synthesis complicated this line of thinking. At the same time, others argued that the fat-soluble nature of oily THC resembles common anesthetics that work by dissolving into the fatty membranes of nerve cells and interfering with conduction of electrical impulses.

There was little benefit in knowing the bare fact that THC is the chemical in marijuana most responsible for getting people high. Being able to repeat an impressively long chemical name – delta-9-tetrahydrocannabinol – does not really bring anyone closer to understanding how marijuana works. A central mystery remained until the mechanism by which THC interacts with the brain and alters its function was discovered.

The next monumental breakthrough came in 1988 from researchers at St. Louis University Medical School. Allyn Howlett and a graduate student, William Devane, announced the discovery of a unique, cannabinoid-specific receptor in the rat brain.[4] While THC can be labeled radioactively, it does not bind tightly enough to this receptor to be a useful probe. By using radioactively labeled CP-55,940, Pfizer's powerful synthetic cannabinoid with more intense affinity for the receptor, they demonstrated that cannabinoid molecules attach to very specific receptor sites that naturally occur in the brain. Howlett and Devane had discovered a clearly defined cellular mechanism to explain interaction between cannabinoid chemistry and biophysiology – the direct linkage between marijuana and the brain!

The mechanism of chemical communication between nerve cells (called neurons) is as remarkable as any of nature's many wonders. Receptors for neurochemicals are complex proteins, over 400 amino acids long, that naturally fold up on themselves multiple times and then float in the thin fatty membrane that encases cells. Each typical receptor crosses the cell membrane seven times, with portions sticking up outside the cell and other portions entering into the cell's interior. The analogy of neuroreceptors to locks that can be opened only by specific keys is quite apt, though an oversimplification, as will be discussed in Chapter 10. Our nervous system brings "keys" (neurotransmitter molecules) and "locks" (receptor sites) together in what are called synapses. Synapses generally consist of an upstream neuron's passing its neurotransmitter across a short distance (20–40 nanometers) to a downstream neuron's receptor sites. For example, when a neurotransmitter such as serotonin or dopamine is released by an electric impulse travelling from a neuron cell body down its long extension (axon) to a synapse, the neurochemical crosses the synapse and slips into its unique receptor site in the next neuron downstream. Like a key opening a lock, the neurotransmitter alters the receptor's shape. This change in the receptor's conformation then allows the passage of ions (typically calcium) into the cell to activate complex events that either stimulate or inhibit its activity. The pattern of stimulation and inhibition passing through the brain from one neuron to another creates a stream of information much like the stream of electric impulses in a computer. The exquisite level of detail being transferred through the brain can literally be *seen* by focusing attention on the dynamic wealth of visual information being passed from your retinas to the back of your brain and then into conscious awareness of whatever you are seeing at any moment. The remarkable speed and detail of neuronal impulses and synaptic activity occurring in the brain can be experienced directly, though we generally take all this for granted.

Howlett and Devane solved the mystery of how THC interacts with the brain when they discovered cannabinoid-specific receptors. In an extreme understatement, they ended the article announcing their discovery by saying, "Thus, the importance of the characterization of a cannabinoid receptor will make a major impact on research in this field."[5] In fact, the cannabinoid receptor they discovered was soon recognized to be the most abundant neuroreceptor in the brain.[6] Neuroscience researchers around the world responded to Howlett and Devane's discovery like thoroughbreds when the bell rings and the gates open at a racetrack.

Since it was highly unlikely that evolution had developed cannabinoid receptors solely for the purpose of responding to marijuana's THC, the horse race to discover the brain's natural cannabinoid neurotransmitter had begun. Mechoulam described his

response to Howlett and Devane's discovery by saying, "We assumed that a cannabinoid receptor is not formed for the sake of a plant that has compounds that bind to it, but for an endogenous [naturally occurring] brain . . . [compound]. I decided to try to identify it."[7] He also recruited William Devane to work at his laboratory at Hebrew University and teamed him with Lumir Hanus, a visiting Czech chemist.

Two important pieces of research in the U.S. were reported by the NIH in 1990 while Mechoulam's team was hard at work trying to isolate the brain's natural cannabinoid. Early in the year, Miles Herkenham reported using radioactively labeled CP-55,940 to map the location of cannabinoid receptors.[8] He soaked slices of brain from several mammalian species (including human) in a solution containing the radioactive cannabinoid and then spread the slices out on radioactive-sensitive film. When he developed the film three to four weeks later, Herkenham had images of where cannabinoid receptors are most densely concentrated. Several conclusions were immediately apparent: first, there was a huge number of cannabinoid receptors in the brain; second, their unique distribution was the same across several different species; and third, by matching an area of the brain that is densely populated by cannabinoid receptors with the mental functions known to be related to that specific area (for example, the hippocampus and memory), we can begin understanding why marijuana produces its unique effects (explored in detail in the next chapter). Herkenham had mapped the brain areas that give rise to pot's characteristic high when stimulated by THC. He also observed that "sparse densities in lower brainstem areas controlling cardiovascular and respiratory functions may explain why high doses of delta-9-tetrahydrocannabinol are not lethal."[9] In other words, pot does not interfere with breathing like opiates do, too often with fatal consequences.

The other discovery at NIH in late 1990 involved cloning the cannabinoid receptor by Lisa Matsuda.[10] Her work demonstrated that human chromosomes possess the DNA for building cannabinoid receptors and she described the receptor's exact structure. By cloning the DNA, she enabled researchers to produce cannabinoid receptors in unlimited numbers, which facilitated searching for natural cannabinoid compounds in the brain that would activate these receptors. The hunt was circling more tightly on a possible endogenous (i.e., produced within) cannabinoid in the brain.

To anyone who had followed the endorphin story, the trail of research involving cannabis looked familiar. In both cases – poppies and cannabis – the active mind-altering ingredients were purified from plants and radioactively labeled to search for receptors in the brain. In the case of poppies, researchers soon found opiate receptors and endogenous morphine-like neurotransmitters (endorphins, for short) produced by the brain. An entire endorphin *system* exists, including receptors and all the enzymes needed to synthesize and metabolize natural opiate neurotransmitters. It was growing apparent that the same was also being found to be true for an endogenous cannabinoid (endocannabinoid, for short) system. Both Herkenham and Matsuda explicitly referred to this likelihood in their papers, and Mechoulam's laboratory was about to verify this reality.

Raphi's "mixed bag"[11] of researchers at Hebrew University of Jerusalem, "Moslem and Christian Arabs, observant and non-observant Jews . . . a German and an American" (William Devane) published a report of the first isolation of the brain's natural cannabinoid in 1992.[12] Devane was studying Sanskrit at the time and chose the name "anandamide," which means "supreme joy, or bliss." Mechoulam explained their choice of the

name as being one that only a dedicated laboratory researcher might make when feeling the special joy of being the first to make a significant scientific discovery. "We were quite happy to discover the compound," he said in a gross understatement. And he joked that they did not use a Hebrew name "because in Hebrew there are not so many words for happiness . . ."[13]

Isolation of the first brain cannabinoid, anandamide, identification of its structure, and confirmation of its cannabinoid properties required expertise in multiple disciplines, which illustrates the need for a team of diverse researchers. They first developed a unique radioactively labeled synthetic cannabinoid and mixed it with synapses containing cannabinoid receptors concentrated from rat brains. The question was: could they extract anything from brains to add to the solution of synapses that would bind to the cannabinoid receptors and thus leave fewer open receptor sites for the radioactive cannabinoid to attach to? If less radioactively labeled cannabinoid was able to bind with receptors already occupied by the natural cannabinoid they had extracted, it would be washed out and the total radioactivity of the solution would be reduced. The team knew the endocannabinoid they were looking for would be a fatty substance and searched for the lipid using a technique called thin-layer chromatography (TLC). The principle of TLC can be seen whenever you splatter grease on a nice shirt and it begins spreading out from where it first landed. Since different compounds "travel" at different speeds, Mechoulam's team was able to separate lipids from ground up pig brains into finer and finer extracts. By a process of successive approximations, they continued to concentrate the portion that competed with the radioactive synthetic cannabinoid for cannabinoid receptors. In the end, 4.5 kilograms (almost 10 pounds) of brain yielded 0.6 mg (0.000021 ounces) of the substance they called anandamide – the first natural endocannabinoid discovered (others soon followed, though with more mundane names, e.g., 2-AG).

A new chapter in marijuana research dawned with the discovery of anandamide, and research interests split into two parallel, only partially overlapping paths. Basic neuroscience researchers explored one path by focusing on the brain itself. They investigated the role this newly discovered endocannabinoid system plays in normal brain function. What does the endocannabinoid system contribute to the body's normal physiology? Why does our DNA contain instructions for enzymes to synthesize and metabolize anandamide and to build natural cannabinoid receptors? While fascinating basic discoveries have poured into the neuroscience literature, far more questions have been generated than answers. Basic research into the endocannabinoid system will remain on the exciting cutting edge of neuroscience for the next few decades.

Researchers primarily interested in marijuana took a different path. They focused on the remarkable similarity in the three-dimensional structures of anandamide and THC. The U.S. National Institute of Drug Abuse (NIDA) provided a dramatic comparison of the two molecules on its website (www.drugabuse.gov/publications/research-reports/marijuana/how-does-marijuana-produce-its-effects) (Figure 1.2).

Researchers immediately understood that marijuana affects our brain because the THC it contains is a great mimicker of endogenous cannabinoids. The brain cannot distinguish between the THC in marijuana and its own natural cannabinoid chemistry, which forms the basis for both recreational and medicinal marijuana use.

On the recreational side, researchers focused on the human consumption of marijuana and began eagerly exploring what happens when THC activates our

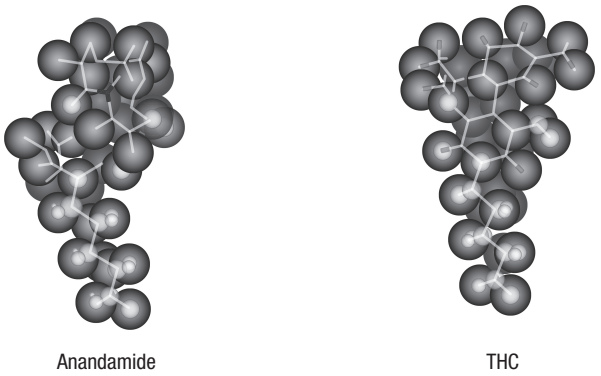

Figure 1.2 Comparison of anandamide and THC molecular structure. Source: NIDA. www.drugabuse.gov/publications/research-reports/marijuana/how-does-marijuana-produce-its-effects.

endocannabinoid system. Exactly how do molecular events result in the cannabinoid experience of being high? Once THC fits into receptors designed by evolution for anandamide, does it unlock the receptor any differently than anandamide, any wider, or longer? And what are the consequences of consistently activating our cannabinoid system with THC weekly, twice a week, or even daily?

On the medicinal side, researchers wondered how modifying endocannabinoid activity reduces pain and suffering, and even treats some human diseases. They began taking their lead from folk medicine and anecdotes about marijuana's medicinal benefits. First, researchers put these claims to the test by applying the scientific method to move from mere opinion to objective, reproducible fact. Second, as basic research better understood our endocannabinoid system, research could begin exploring the mechanisms by which the chemistry in marijuana exerts its beneficial effects, as well as its negative side effects.

Before the impact of marijuana on the brain, whether used recreationally or medically, can be explored further, some necessary additional detail about the uniquely central role the natural endocannabinoid system plays in regulating brain function must be understood. The discovery of an entire endocannabinoid *system*, composed of neurotransmitters and receptors, ignited an international explosion of neuroscience research. In 1993, Sean Munro at the University of Cambridge, UK, discovered a second cannabinoid receptor in the rat spleen, with no evidence of its presence in the brain.[14] The original receptor identified in 1988 by Howlett and Devane now became referred to as the CB1 receptor. Because CB1 receptors are found primarily in the brain and the newly discovered CB2 receptors are found primarily in the immune system and other parts of the body, the two began being called central and peripheral cannabinoid receptors respectively, though later research has found CB2 receptors in the brain under some conditions.

The following year, Vincenzo Di Marzo in Paris and colleagues in Italy and California reported that anandamide is produced from a precursor present in all cell walls – the polyunsaturated fatty arachidonic acid.[15] Like Mechoulam, Di Marzo had immediately recognized the chemical structure of anandamide closely resembles this ubiquitous building block for the lipid membrane surrounding cells. Cell membranes are essentially films of fatty acids. Oil and water do not mix, so a fatty membrane is an effective barrier for separating the watery inside of cells from the watery outside. The existence of

anandamide's precursor in cell membranes is distinctly different from how neurotransmitters are typically formed and stored. Neurotransmitters such as serotonin, GABA, and dopamine are synthesized in the neuron cell body far from where they are released. After synthesis they must first be transported through the cell's axon to be stored near synaptic connections with other neurons. Small electrical disturbances running down the axon's outer membrane trigger release of the neurotransmitter into the synapse. We typically say that the neurotransmitter is released when a neuron "fires."

Di Marzo's investigation of neurons in culture found that anandamide is synthesized from the arachidonic acid in cell membranes in response to calcium ions that typically flow into cells through receptor sites unlocked and opened by their unique transmitter molecule. A variety of typical neurotransmitters locking into their receptors were all found to activate the synthesis of anandamide from the arachidonic acid in cell membranes. The life span of anandamide once released into the synaptic space outside the cell is short due to rapid cellular reuptake and degradation. Di Marzo concluded that anandamide's action within the brain depended on its reaching cannabinoid receptors located somewhere on neighboring cells. The exact location of this interaction between endocannabinoid and CB1 receptors was still unknown.

While Di Marzo was investigating the synthesis of anandamide, Mechoulam's exploration of the newly identified peripheral CB2 cannabinoid receptor discovered a second endocannabinoid in 1995 – 2-arachidonyl glycerol (2-AG).[16] Reasoning from the existence of several peripheral cannabinoid effects (e.g., bronchodilation, decreased intraocular pressure, and intestinal calming), Mechoulam assumed that endocannabinoids would be found in both brain and the rest of the body. After extracting 2-AG from dog intestines, he demonstrated that it satisfied the cannabinoid tetrad when administered to animals, i.e., decreased spontaneous activity, pain reduction, lowered temperature, and immobility. Furthermore, anandamide was absent in the gut extract. The endocannabinoid system, now consisting of at least two different receptors and two different neurotransmitters (there would eventually be more), was rapidly growing in complexity. By 1997, Nephi Stella, a postdoctoral fellow at the Neurosciences Institute in San Diego announced that 2-AG exists in the brain as well and measured it in amounts 170 times that of the more poetically named anandamide.[17] Exploration of our brain's endocannabinoid system was rapidly picking up speed.

While understanding that an endogenous cannabinoid system exists within the brain and is stimulated by THC's similarity to our natural neurochemistry is important information for health professionals to master, there are a few more essential characteristics of this fascinating system to be understood. At this point many clinicians may fear I am about to get lost in the basic science weeds, so to speak, but I ask readers' forbearance. One more monumental discovery wraps the preceding basic science into a coherent whole with profound implications. Integrating the following information will provide an understanding of how the endocannabinoid system regulates the rest of brain chemistry.

The expanding international scope of research is illustrated by the next stop in the endocannabinoid story – Hungary. Mechoulam's laboratory had discovered anandamide five years before Istvan Katona began his Ph.D. studies at Semmelweis Medical University in Budapest. Katona had attended the prestigious Trefort high school (alma mater of the theoretical physicist Edward Teller, developer of the hydrogen bomb) where university students did their practice teaching. Raised during the communist occupation

of Hungary, Katona pursued a scientific career "because it provided the luxury of intellectual freedom."[18] The newly described endocannabinoid system was the hot topic for neuroscience graduate students needing to make their mark in research. Katona began exploring the microanatomy of this new system and made his mark with a series of groundbreaking papers beginning in 1999.[19]

Neurons are essentially one-celled animals that live throughout an organism's lifetime. Some stretch from the base of our spine down to the end of our toes, over a meter long in very tall people. They can survive independently in a petri dish when given the proper nutrients. The brain is made up of approximately 86 billion of these one-celled animals – quite a can of worms. What makes neurons unique among all our body's different cell types is their ability to communicate with each other and to form complex interconnected networks.

Communication occurs when a presynaptic neuron passes a chemical messenger to receptors on the next postsynaptic neuron. These one-way synaptic connections pass signals along from neuron to neuron to neuron. There are a nearly inconceivable number of synapses in the human brain – roughly 5000 times as many as there are stars in our Milky Way galaxy. The predominant flow of information throughout the brain occurs by passing chemical messengers downstream across synapses from one separate neuron to the next.

Istvan Katona's contribution was to localize endocannabinoid receptors, not just where they are found in the brain (Miles Herkenham had done this), but also more specifically where they exist on each neuron. He argued that this was the only way to know the mechanism of action of both marijuana's THC and the brain's natural cannabinoid chemical messengers. He followed a path suggested by two pieces of research. First, it has long been known that a brain area shaped like a seahorse called the hippocampus is crucial to learning and memory. The hippocampus is the scratch pad substrate for our short-term memory. It creates a neural model for information that is then uploaded into longer memory storage. Without a functioning hippocampus, no memories are stored – a condition called Korsakoff's Syndrome seen in end stage alcoholism. A temporary functional Korsakoff's is experienced when binge drinkers "blackout" and have no memory the next morning for the night before. While marijuana users do not experience anything as extreme as blackouts, they do commonly experience difficulty with short-term memory. Careful cognitive studies, reviewed in detail in a later chapter, have documented the reality of learning and memory decrements during THC intoxication. The second piece of research was Herkenham's work showing a very heavy concentration of CB1 receptors in the hippocampus. Where there is smoke, Katona hypothesized, there may be interesting fire.

Katona used electron microscopy to examine hippocampal slices stained with gold-labeled antibodies to CB1 receptors and found that the gold particles were located *pre*synaptically, not *post*synaptically as typical receptors are. He describes the moment of discovery as "fantastic, I will never forget seeing [the receptors] in the electron microscope, it was indeed a Eureka moment, which made me addicted to neuroscience research."[20] His words echo Rafael Mechoulam's bliss at discovering anandamide – the profound joy and awe of being the first human to observe one of nature's previously hidden secrets!

The presynaptic location of CB1 receptors means that the endocannabinoid system is not structured to pass information downstream from one neuron to the next, but rather

to provide feedback to upstream neurons. This simple fact turns everything about the endocannabinoid system on its head and makes sense of Di Marzo's discovery that activation of a variety of receptors by their corresponding neurotransmitters sets the synthesis and release of anandamide in motion. The endocannabinoid system is not simply one more typical neurotransmitter system. The endocannabinoid system does not fit the usual model for passing information downstream from one neuron to the next.

Katona's research went a step further in describing the functional impact of the presynaptic location of CB1 receptors. Electrical stimulation in the hippocampus of the presynaptic neurons upon which the CB1 receptors were located led to the release of the neurotransmitter called GABA. When Katona activated the CB1 receptors with a powerful synthetic cannabinoid (WIN 55,212), electrical stimulation no longer released the GABA. To be sure that cannabinoid stimulation was the direct cause of turning off the GABA neuron, he repeated the experiment after pretreating the CB1 receptors with a recently developed cannabinoid blocker SR141716. Once CB1 receptors were blocked, WIN 55,212 could no longer activate them, and electrical stimulation again released GABA.

While the research described above may be confusing, and more detailed than most need to remember, the conclusions Katona reached should be clear. *The endocannabinoid system acts as a negative feedback system designed to modulate nearly all the other neurotransmitters in the brain.*[21] CB1 receptors in the brain consistently appear to be presynaptic and "activation of presynaptic, CB1 receptors always results in the attenuation of neurotransmitter release."[22,23] In a 2008 paper Katona and Tamas Freund elaborated on this idea by describing the function of the endocannabinoid system as a "circuit breaker" in the brain.

The endocannabinoid system is fundamentally a neural homeostatic mechanism. Homeostasis simply means that biology has provided us with multiple ways of maintaining a constant internal environment. For example, if we get too hot, we perspire to cool ourselves. If we drink too much water, we urinate more. In the case of brain activity, if a neuron gets too active and releases large enough amounts of neurotransmitter, negative feedback by the endocannabinoid system reduces the amount released by the presynaptic neuron. Our natural cannabinoid system works to stabilize brain activity. While this sounds good, and maybe even sounds like a reason to consume the phytocannabinoids offered by marijuana, the story is never that simple when dealing with biology. Complications caused by external stimulation of the endocannabinoid system by marijuana use, especially on a regular basis, will be reviewed in later chapters.

The endocannabinoid system needs to be seen as always active to one degree or another. Like a dripping faucet, the activity is either increased or decreased in response to the level of presynaptic neuronal activity. In other words, our endocannabinoid system is a "tonic" system – it has a tone (similar to a muscle's tone) that can be altered. The normal, physiological stimulus for altering endocannabinoid tone is the release of neurotransmitters from a presynaptic neuron. Activity produced within the postsynaptic neuron by arrival of the neurotransmitter (i.e., influx of calcium ions) initiates the synthesis of anandamide and 2-AG from the lipids in the cell membrane. Although enzymes begin breaking them back into their components soon after synthesis and release, if the presynaptic neuron is firing rapidly, enough endocannabinoids are produced that some diffuse back across the synapse and reach the presynaptic CB1 receptors. When the cannabinoid receptors are activated, they initiate events within the presynaptic

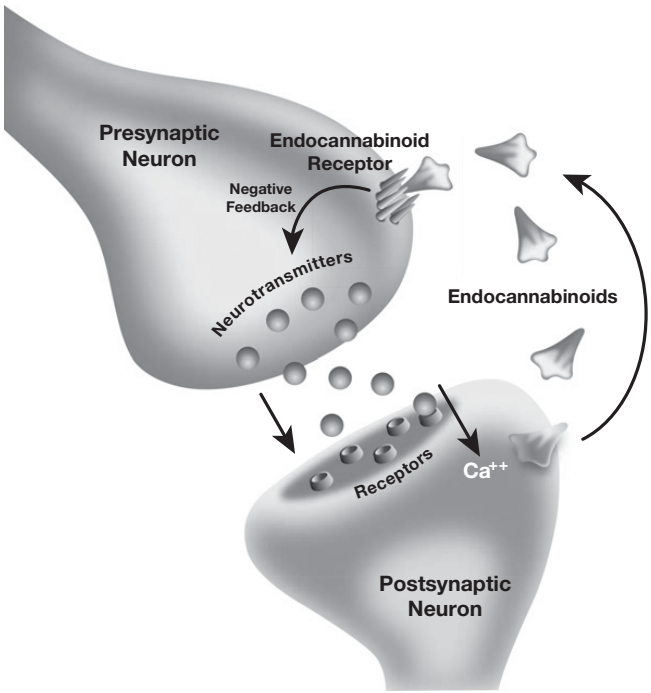

Figure 1.3 Presynaptic structure of the endocannabinoid system. Source: Image based on Katona, J., et al., "Presynaptically Located CB1 Cannabinoid Receptors Regulate GABA Release from Axon Terminals of Specific Hippocampal Interneurons," *Neurosci*, (1999); 19(11):4544–58.

neuron that reduces the amount of neurotransmitter being released with each firing. This negative feedback re-establishes homeostasis for the postsynaptic neuron, like turning down a dimmer switch on a light bulb that had grown too bright.

A second way to activate cannabinoid receptors is by flooding the brain with cannabinoid molecules from the outside, i.e., by ingesting marijuana products. When people smoke marijuana, the cloud of THC reaching CB1 receptors substantially increase cannabinoid tone throughout the brain. The effect is to reduce the release of neurotransmitters from all presynaptic neurons containing CB1 receptors. In this case, however, the effect is the loss of homeostasis. Brain chemistry is shifted far from its normal equilibrium. While this might sound ghastly and dangerous, it is generally temporary, safe, and considered delightful by many people.

Sometimes a picture is truly worth a thousand words and Figure 1.3 illustrates the presynaptic structure of our endocannabinoid system. Let's walk through it step by step.

1. Electrical impulses travelling down the presynaptic neuron release whatever neurotransmitter the neuron is designed to use.
2. The neurotransmitter travels across the synapse and activates its unique receptor on the downstream postsynaptic neuron, causing an influx of calcium (Ca^{++}) ions and thereby either stimulating or inhibiting its activity.
3. In response to these synaptic events, the downstream neuron synthesizes anandamide and 2-AG from fatty molecules in its own membrane.
4. Endocannabinoids are produced on demand, as needed. The amount of anandamide and 2-AG produced depends on the activity of the presynaptic neuron.

5. The endocannabinoid molecules migrate back across the synapse to activate CB1 receptors on the upstream, presynaptic neuron.
6. The activated CB1 receptor provides negative feedback to the first neuron, causing less neurotransmitter to be released with each firing.

At this point, enough detail has been established by thousands of research projects conducted worldwide to produce a coherent overall perspective on the biochemical mechanism by which marijuana interacts with the brain. To review and summarize: The THC in cannabis mimics an important element of our brain chemistry. The cannabis plant and the marijuana harvested from it are innocent bystanders. No one knows how or why THC exists in the cannabis plant (and no other), although it is highly unlikely that cannabis developed THC in order to please humans. The endocannabinoid system acts as a rheostat, using negative feedback to keep the activity of all other neurotransmitters in their proper range, neither excessive nor insufficient. It is, therefore, a highly significant homeostatic mechanism for our brain and, by extension, our mind. In other words, a properly functioning endocannabinoid system is essential for our brain chemistry to be well balanced. Now, with an understanding of basic endocannabinoid system science in hand, I can turn attention to how changing the brain with marijuana changes our experience.

Susan

At 14 years old, the girl sent to me by her worried parents was sure I had nothing to tell her that she had not already heard from her parents. I started by asking if she was in my office because she wanted to be or because her parents forced her.

"Duh," she challenged.

"Duh?" She remained silent. "There's a thousand kinds of 'Duh'. Which is this one?"

"You're going to do what my parents hired you to do."

"Which is?"

"To get me to stop smoking weed."

"I made it clear to your parents that I don't have the power to do that. I told them I would see if I could tell you some things about marijuana you might find interesting. So you understand how it works."

"I understand. It's delta-9-tetrohydrocannabinol – THC – that gets you high." She threw out the chemical name like the cognoscente she saw herself to be.

"And do you know how THC works?" I asked as neutrally as I could and saw she felt challenged, but was curious enough about what I might say next that she parried.

"Do you?"

"Yes, and the story is fascinating." I waited.

"Yeah?"

Engaging a patient's curiosity is one avenue for developing a workable relationship. Susan had just let me know she was curious.

"Do you want me to tell you what I know?" It is always important to ask permission in order to reduce the possibility that someone will feel intruded on by the information I provide.

"Yeah."

She had not only given permission, but had in essence asked to hear more. The door was open and I began telling her about the wonder of our having not only receptor sites for

marijuana but also our own marijuana chemistry that THC mimics. That's the beginning of understanding how marijuana works!

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Chapter

2 Marijuana's Acute Effects
From Brain to Experience

Some people may ask, "Once marijuana users learn it affects the brain's chemical balance, why do people keep using it?" The answer is as old as the human species. Altering consciousness is a primary source of pleasure for most people, whether through excitement on a roller coaster, relaxation through prayer and meditation, the thrill of black diamond skiing, drugs, or any of a myriad other possibilities. Almost everyone spun around and around as a kid in order to stagger about, lose balance, and fall down. Why? Because it was fun! There was nothing immoral about having someone twist the swing we sat on until we spun into crazy dizziness when they let go. Then, when recovered, we asked to do it again. Fun – though most of us did stop spinning to get dizzy at some point. And most people who ever use marijuana also stop at some point, including 82% of those who had ever used at least 10 times stopping by age 34.[1]

In this chapter we pull back from the level of individual neurons and begin exploring how marijuana's impact on the brain produces the experience of being high. It is not satisfying enough to know THC "tickles" natural cannabinoid receptors. People are more interested in how this makes them *feel*, and why. The following information explains the different facets of being high and also prepares people to understand the flies in the ointment described in the next chapter. Understanding exactly how marijuana impacts the brain to make us feel high is fascinating to many users. And understanding how *regular* use of marijuana impacts the brain can also generate powerful cognitive dissonance for many, but this is getting ahead of ourselves and will also be covered in the next chapter.

For now, in order to understand the sensation of being high, it is useful to return to Miles Herkenham's work in 1990 locating the densest concentrations of CB1 receptors in the brain. Different areas of the brain specialize their structure and connectivity in order to serve different functions. We would therefore expect that functions arising from areas

with the highest concentrations of cannabinoid receptors would be the most significantly impacted by THC. Each of these areas underlies different facets of our experience with marijuana. Let's look at one area at a time, starting with the hippocampus and then proceeding to the amygdala, and the basal ganglia/cerebellum. Two additional areas, the frontal cortex and the reward circuitry will be dealt with in later chapters.

The Hippocampus

Nearly everyone who has used marijuana has experienced disruption in short-term memory. This disruption is often the source of considerable amusement. When stoned, by the time people near the end of a sentence they can forget what they set out to say. Predicates veer far from subjects and sentences simply dissolve into confusion and laughter. This effect appears to be more intense in beginning users and contributes to conversations that ramble across a lot of disconnected terrain. Loss of short-term memory is partially responsible for the perception of marijuana users being "airheads." With practice, many users feel that their memory is not as impacted as it was initially. It is not often clear how much of this perceived improvement is a practice effect, a result of developing compensatory mechanisms, something more basic in their brain's physiology, or merely denial.

Memory is obviously essential for learning and a host of studies document decreased memory and learning with acute marijuana intoxication.[2] THC ingestion prior to being presented a list of words impairs immediate and delayed recall in a dose-dependent manner. In particular, cannabinoids increase intrusion errors – the inclusion of irrelevant information in what is "remembered." Memory disturbances are greatest during periods of peak THC blood levels, which depend on the mode of ingestion (whether inhaled or swallowed). Studies that include a structured rehearsal of newly presented information do not improve memory performance. On the other hand, most studies show no impairment in recall of information learned before being given THC. Tasks dependent on short-term memory are also impaired. The Digit Symbol Substitution Test of working memory is highly sensitive to THC. This timed test resembles a decoding task by providing a key of numbers paired with symbols (e.g., 1[-] . . . 9[=]) at the top of the page and people are instructed to copy the corresponding symbol beneath rows of numbers lower on the page. THC increases errors and slows speed in this test of working memory.

Animal studies have the disadvantage of not being able to use word lists to test memory, but they have the advantage of being able to inject cannabinoids and blockers directly into the hippocampus. The most robust effects of THC are on working memory and short-term memory, often demonstrated in an animal's ability to learn and remember the path through mazes. Squirting a cannabinoid into the hippocampus causes the same memory deficits as administering it by ingestion; and adding a cannabinoid blocker reverses the effects, which proves the critical role of CB1 receptors in this specific brain area.

Fascinating research by J. P. Terranova in France investigated social memory and learning among a colony of rats.[3] Adult rats greet juveniles by sniffing their snouts to create an olfactory memory that can last for a couple hours. If the rats are separated longer than two hours, the whole sniffing routine needs to be repeated. When adult rats are given THC before encountering a juvenile, they hold onto their memory of the other

for a much shorter time. However, if the adult rats are first given the cannabinoid blocker SR 141716 before the THC, no decline in memory occurs. All of this demonstrates again that THC decreases memory, but the next step by Terranova broke into new territory. Aged rats (two years old) naturally show a decline in their social olfactory memory. They are unable to sustain the memory for two hours like younger adults. However, when the cannabinoid blocker was given by itself, older rats showed an improvement in their memory. In other words, reducing cannabinoid tone (i.e., lowering endocannabinoid activity) improved memory – in elderly rats.

Terranova's research clearly demonstrates that our endocannabinoid system *modulates* short-term memory on an ongoing basis. With more cannabinoid activity short-term memory shortens; with less cannabinoid tone short-term memory lengthens. Why did mammals evolve a mechanism to shorten or lengthen scratchpad memory, you might wonder? Perhaps this modulation is useful because we encounter different tasks in life, some of which are more efficiently performed with a longer short-term memory, and others with shorter short-term memory. For example, when we are given a number over the phone but have to hunt for a pen to write it down, our short-term memory needs to stretch out until we find the pen. On the other hand, if a basketball player's mind is still remembering what happened 10 seconds ago at the other end of the court, he or she may not be able to respond effectively to what is happening right now in front them. Working with a very short short-term memory may improve competitiveness by keeping athletes more fully in the present moment. I have seen professional basketball players forget the play called during a timeout by the time they get back on the court, so the shift in length of short-term memory may not be instantaneous.

The phenomenon of forgetting is another example of the important role of increased cannabinoid tone. In Raganthan's words, if every impression "is instantly stabilized and consolidated, then it is possible that the brain's computational space will be quickly consumed by useless/irrelevant information leading to rapid saturation of processing and storage capacity. Perhaps the endocannabinoid system ... contributes to the mechanisms that prevent the automatic and instantaneous consolidation of memory."[4] In other words, forgetting may be a basic and essential element in learning. This paradoxical phenomenon was demonstrated in a study of mice genetically altered to eliminate the DNA coding for CB1 receptors (called CB1 knockouts). Mice without CB1 receptors continue to follow a path through a maze that they had previously learned at the expense of learning a new one.[5] A functional endocannabinoid system with well-balanced tone may be necessary to forget unneeded memories – to wipe the slate clean – in preparation for new learning. The basic conclusion reached by researchers is that endocannabinoids are an important modulator of memory. More about this in Chapter 6 on regular, heavy use of marijuana.

The Amygdala

There is a small almond sized collection of neurons in the temporal lobe bilaterally called the amygdala. Together with the hippocampus, these two brain areas were among the first to develop when mammals evolved. The amygdala is a very old portion of the "new brain" and it is a treasure trove of cannabinoid-based experiences, from appetites to emotions, our sense of novelty, and important global characteristics of consciousness such as awe. Activity in the amygdala can hijack our reason, throw us into panic and

fight-or-flight action, or sooth us like a baby. The stimulation marijuana gives our amygdala accounts for most of the reasons people enjoy getting high.

The amygdala, together with an ancient structure at the core of premammalian brains called the hypothalamus, is intimately involved in regulating our appetite for food. The amygdala and hypothalamus are interconnected and both are rich in CB1 receptors. Multiple researchers have proven what is obvious to most people who have ever used marijuana – pot produces the "munchies." Enhancing cannabinoid activity has been proven to stimulate appetite in cancer and AIDS patients experiencing wasting syndrome.

Marijuana does not globally increase appetite, but rather seems to increase the motivation to eat comfort foods. Many marijuana users tell tales of ingesting a variety of delicious delicacies, from brownies, cookies, and Sweet Tarts to more finely prepared meals. Indeed, two researchers jumped right into the heart of the matter by giving rats THC and then offering a choice between regular rat chow and chocolate cake batter. In a stroke of understatement, after watching the stoned rats gravitate toward cookie batter, they concluded that THC increases "palatable" food intake.[6] While the reason for this might appear obvious to any marijuana users, a deeper story has emerged.

Since stimulating the endocannabinoid system (i.e., increasing cannabinoid tone) causes the munchies, it seemed logical that reducing cannabinoid tone might lessen appetite. And, indeed, animals given the cannabinoid blocker SR141716, generically known as rimonabant, reduced their food intake. The pharmaceutical company Sanofi-Aventis pioneered rimonabant's use in Europe under the brand name Acomplia and began marketing it for the treatment of morbid obesity in 2006. Results after a year seemed promising both for weight loss and a reduction in tobacco use. One can only imagine the financial benefit to the pharmaceutical industry if a single medication could both reduce smoking and curb appetite. Acomplia was described as "generally well tolerated with mild and transient side effects." The theory was correct. Reducing endocannabinoid activity in humans produces the "anti-munchies."

Unfortunately, blocking the endocannabinoid system soon proved more dangerous than blocking our endorphin system. Many patients have been given the long acting opiate blocker naltrexone for a variety of purposes and it has truly been well tolerated by most with only "mild and transient side effects." But Acomplia had to be pulled from the market in 2008 due to multiple reports of serious depression. Side effects made cannabinoid blockade a failure as a weight loss drug, but the results opened up a perspective on depression that is still being explored.

The depression caused by Acomplia should not be surprising. Marijuana has a long history of being used to elevate mood, reduce anxiety, and alleviate stress. The Acomplia experience documents that a well-functioning, balanced endocannabinoid system is essential for maintaining normal mood – euthymia. Development of mice that lack CB1 receptors added more evidence to the critical role of a well-functioning endocannabinoid system for emotional health. Without a functioning endocannabinoid system, the mice weigh 24% less at 20 weeks old[7] and show heightened sensitivity to stressful stimuli and behavioral evidence of anxiety and depressive helplessness.[8] While all this evidence would initially suggest that marijuana's THC would be an effective antidepressant medication, our brain is too complex for such a simple solution. We will return to the topic of marijuana and depression in Chapter 10 on potential cannabinoid medications.

A more immediate topic involves research into the role of our endocannabinoid system during the first days of life outside the womb. An Israeli researcher, Esther Fride, reviewed the mounting evidence that appetite, especially for "comfort foods," is a reflection of the level of endocannabinoid activity.[9,10] She even noted that the function served by endocannabinoids in the most primitive creature possessing a neural network, the hydra, involves a feeding reflex.[11] Cannabinoid stimulation causes the hydra's "mouth" to close around food collected by its tentacles. Fride put all this together with two interesting facts: (1) The highest levels of 2-AG and CB1 receptor synthesis occur in brain structures associated with feeding behavior on the first day of life; and (2) Relatively high levels of 2-AG are expressed in human breast milk. Is it possible, she wondered, that the endocannabinoid system is a major stimulus for the first episode of milk suckling in newborns?

Fride explored this possibility by giving the cannabinoid blocker SR141716 to newborn rat pups in the first day of life. They all failed to suckle and died, even though their mothers increased the licking that normally stimulates suckling. A functional, well-balanced cannabinoid system is important for the very existence of mammals. After breathing, the next most important behavior for a newborn mammal is suckling – attaching to mother's breast and feeding. The "newborn munchies" are critical to survival. Is it any wonder that THC's strong stimulation of brain CB1 receptors later in life stimulates craving for comfort food? Perhaps cannabinoids are even part of the emotional phenomena of bonding and Erik Erikson's first stage of development – establishing basic trust in the world. After all, marijuana has been called the "love drug." While purely speculative, these thoughts are consistent with the scientifically proven importance of endocannabinoids for suckling to occur. Is it possible that re-experiencing a high cannabinoid state brings some people soothing affective reminiscence of earlier infantile comfort, connectedness, and trust?

An additional element may play into the unique quality of cannabinoid-induced appetite. Hypothalamic neurons that promote satiety are also stimulated by beta-endorphin released by the action of external cannabinoids.[12] When the activation of satiety neurons is reduced by the rapid, short acting opioid blocker naloxone, external cannabinoids no longer stimulate appetite. While it may be difficult to imagine the experience of being both hungry and satisfied, this paradoxical combination characterizes the munchies that typically occur when high – the delicious drive to feel "more of enough."

The amygdala contributes greatly to regulating our emotional life. Its connection to the autonomic nervous system permits the amygdala to generate full body experiences of profoundly calming and intensely activating emotional states, including panic and fight-or-flight responses. The impact of marijuana on anxiety levels, however, is complex. To begin with, some people are made anxious by any amount of marijuana, naïve users are more likely to feel anxious, and most people feel relaxation at low doses and are more likely to feel anxious at higher doses.[13] Furthermore, set and setting have a great deal to do with determining whether marijuana causes anxiety. Set refers to a person's expectations. Someone who considers marijuana to be a dangerous drug is more likely to filter their pre-existing anxiety into the drug's effect on them. Setting refers to the environment in which marijuana is consumed, whether within a safe circle of friends, surreptitiously used to avoid detection by disapproving parents, or in the neutral coldness of laboratory conditions. And furthermore, many patients have related developing increased anxiety

over their life span, even with only occasional use. Whether this increasing vulnerability to THC-induced anxiety is related to the normal reduction of CB1 receptor density with aging is not known.[14] And finally, more rigid, cautious personalities may be more prone to feeling anxious with perceived loss of their normal mental state with the onset of THC's effects, while novelty seeking personalities may experience this with excitement and curiosity rather than anxiety. These different personality types may be a reflection primarily of the genetically determined density of CB1 receptors in the amygdala.[15]

In addition to the complication of marijuana's biphasic relationship to anxiety, the ratio of THC and CBD is also an important determinant of whether specific strains of marijuana are more activating and anxiety-provoking or calming. An absolute wealth of anecdotes promulgated by the Internet, books, and marijuana dispensaries are in substantial agreement about the difference between marijuana with low versus higher CBD levels. For example, Martin Lee in his book *Smoke Signals* writes, "Cannabidiol balances out the buzz and softens out the euphoria – or, in some cases, the dysphoria – induced by THC, which, in concentrated form, can make people very loopy and weird. CBD is the yin to THC's yang."[16]

Researchers have too often either been unaware of the THC/CBD ratios in the marijuana used in experiments, or they have provided pure THC alone, particularly in animal studies. Raphael Mechoulam has described a phenomenon he calls the "entourage effect," which means that the impact of both phytocannabinoids and endocannabinoids is often modulated – either potentiated or mitigated – by the presence of other related molecules that have no direct cannabinoid activity themselves.[17] As such, the impact of mildly psychoactive CBD on THC is not a true entourage effect. CBD is considered to be a partial antagonist of THC, reducing many of its less desirable qualities.[18] Although researchers continue work at better clarifying the molecular mechanisms of CBD's effect on THC, medical marijuana advocates have latched onto the concept of an entourage effect and often use it loosely to argue in favor of using whole plant products as a herbal medication rather than more pharmaceutical approaches to extracting and modifying the plant's essential ingredients. The science underlying Mechoulam's entourage concept will be explored in more depth in Chapter 10 on the medical uses of marijuana.

Despite all the complexities outlined above, the majority of marijuana users feel "chilled out" when high. They may not spontaneously describe a reduction of anxiety, but they do feel "de-stressed" and less tense. Many distinguish the calming effect of marijuana from that of alcohol, pointing largely to less obtunding of consciousness with marijuana.

The amygdala also creates our sense of novelty. The experience of novelty, illustrated by the sudden appearance of a new font, e.g., Chalkduster, captures our attention. Some people may be energized and enlivened by the sudden appearance of novelty, while others may draw back, disturbed and cautious. It is important to understand that there is absolutely nothing in the above Chalkduster font itself that creates such reactions. If the whole text used Chalkduster and suddenly a Minion Pro font appeared, it would be equally noticeable as novel. I am belaboring this point to clarify that the sense of novelty does not lie in any sensory stimulus itself. Novelty is experienced when the amygdala responds to a *change*. The amygdala is a continuous comparator of our immediate experience to our recent experience. In response to an unanticipated change, activity in the amygdala draws attention to the new stimulus by adding a "zing" to its perception. Of importance to our understanding of

marijuana is the fact that the endocannabinoid system underlies and modulates the experience of novelty.

When marijuana users describe what they like about being high, most include enjoying a freshening of their senses. Music sounds new and more intricate, colors brighten and become more interesting, flavors of food stand out and are noticed differently. Synesthesia sometimes occurs, leading to feeling a high musical note throughout the body and not merely hearing it. The rock group Pink Floyd made particularly effective use of marijuana's impact on listeners of their music. An example of novelty many marijuana users relate to is the small rainbow appearing on every bubble in a sink full of soapsuds. This delightful rainbow occupies exactly the same position on each bubble. Awesome! Most of us stopped playing with soap bubbles and noticing this rainbow sometime before grade school. We habituated to it, expecting its presence. In a similar way, we are initially aware of a new ring on our finger, playing with it frequently, but then its sensations fall into an unnoticeable, habituated background. The amygdala compares our current experience with the ring to recent past experience with the ring and notices no change. The "zing" of amygdala activity is no longer added to sensations of the ring and our attention goes elsewhere. We habituate.

Since the endocannabinoid system is a central element underlying our amygdala's response to change, it is no surprise that altering cannabinoid activity has an impact on our sense of novelty. Increasing cannabinoid tone by using marijuana lowers the bar for experiencing novelty. Being high *dis*habituates us. Stimuli such as the soap bubble's rainbow become noticed again. Or, as one young marijuana user told me, "A trip down the hall to the bathroom becomes an adventure." The stereotypical scene of someone high for the first time staring into a dandelion with awe is an example of dishabituating enough to again notice the detail of this common flower we had come to see as only a nuisance.

The sense of awe is another experience coming from stimulation of the temporal lobe and amygdala. In the 1930s the neurosurgeon Wilder Penfield pioneered the use of electrical stimulation of the brain in conscious patients to isolate the locus of their epileptic seizures. Surprisingly, people often described a numinous, even spiritual, quality to their experience, and a global sense of wonder, awe, and déjà vu or jamais vu in response to the stimulation. The combination of novelty and awe emerging from the amygdala with high levels of cannabinoid stimulation would be expected to provide considerable pleasure to many people's use of marijuana and probably contributes to the sense of spirituality many experience when high.

One major theme in this book is that research originally focused on marijuana morphed into brain research after discovering our endocannabinoid system. The question for neuroscience became one of trying to understand the underlying function of our natural cannabinoid chemistry. This theme is particularly well illustrated by the Belgian Koen Van Laere's research on the relationship between temperament and the endocannabinoid system.[19] Temperament refers to stable biopsychological traits such as biorhythms, emotional reactivity, and introversion/extroversion that are genetically determined. Van Laere discovered that novelty seeking is dependent on the density of CB1 receptors in the amygdala. There are genetic variations in CB1 receptors in the amygdala with low baseline CB1 receptor activity leading to a high novelty seeking.[20] People born with low CB1 receptor activity are relatively unconstrained in their novelty seeking. Their amygdala responds less, leading them to seek greater levels of novelty. On

the other hand, people born with high levels of CB1 receptor activity are more constricted in their response to novelty. The greater responsiveness of their amygdala to novel stimuli leads them to withdraw from too much novel stimulation. Neither constrained nor unconstrained temperament is better than the other. Each merely confers different talents and challenges on individuals.

Van Laere's fascinating discovery has nothing to do with marijuana directly. It is pure neuroscience. On the other hand, it may give some important clues as to why some people gravitate toward using marijuana while others are rendered more anxious, and even paranoid, by smoking weed. And, as we shall see in the next chapter, Van Laere's work may help explain why the tendency of regular marijuana use to reduce CB1 receptors, called downregulation, might lead to changes in temperament and personality.

The bottom line regarding the effect of marijuana on the amygdala is what I call "Virtual Novelty." Marijuana creates the experience of novelty without needing the presence of true novelty. Marijuana enables enjoyment of walking through a redwood forest or the same video game over and over as though it is "new" each time. It enables laughter at the fourth or fifth time you watch an episode of the Simpsons, as though the jokes were still fresh. Novelty is generally a very enjoyable experience. Many people travel to new lands to experience the truly novel. Meditators work to still the mind in order to respond freshly to the world. There is a lot to be said for maintaining the ability to respond with wonder to everyday experience. This is one of the legitimate goals of mindfulness practice. But virtual novelty is a mere simulacrum of the truly novel. Nothing new is actually being experienced, and nothing new is being learned. On the other hand, it *is* fun – a seemingly perfect antidote for the plague of adolescence – boredom. And more than a few people have been reawakened to the wonder of our world by marijuana's momentarily lowering the bar for experiencing novelty.

There is yet one more reason why marijuana's stimulation of CB1 receptors may not lead to new learning. Not only does marijuana interfere with memory formation in the hippocampus and lead to repetition of activities enhanced by virtual novelty, but its impact on the amygdala also directly aids in the forgetting of aversive, i.e., painful and uncomfortable, experiences. The Italian Giovanni Marsicano, while working at the Max Plank Institute in Munich, Germany, demonstrated in 2002 that the endocannabinoid system specifically promotes forgetting negatively charged memories.[21] Marsicano used classical conditioning with mice, first sounding a tone and then sending an electric shock through the floor. Mice soon learned to freeze when they heard the tone. Next, he stopped shocking the mice after sounding the tone. As mice learned that the shock was no longer being delivered, the freezing behavior gradually extinguished. After measuring how long extinction normally takes, he repeated the experiment after administering the cannabinoid blocker SR141716. With CB1 receptors blocked, extinction of the painful memory took much longer, despite increased endocannabinoid levels appearing in the amygdala. The delay was dose-dependent, meaning that a little blockade caused a short delay in extinction, while larger doses caused longer delays. He also explored the extinction of memories created by positive rewards. For example, a tone followed by availability of a food pellet caused mice to run to the feeding lever with each tone. After pellets were no longer given following the tone, the lever pressing behavior gradually extinguished. In the case of learning reinforced by positive reward, pretreatment with the cannabinoid blocker did not change extinction rates. Our endocannabinoid-based forgetting is specifically a balm for painful memories. Perhaps this contributes to the euphoric recall characteristic of marijuana use. People have often told me

that their memories of being paranoid while stoned when waiting to get into a concert ("Is this the right night?" "Are our tickets really good?" "Is that a narc standing behind us?") are not nearly as vivid as memories of the concert itself.

Marsicano concluded the paper reporting his research team's work with the following interesting speculations, which will be explored in the chapter on cannabinoid-based medication: "Overall, our findings suggest that the endogenous cannabinoid system could represent a therapeutic target for the treatment of diseases associated with inappropriate retention of aversive memories or inadequate responses to aversive situations, such as post-traumatic stress disorders, phobias, and certain forms of chronic pain."

Hopefully readers are getting two major points about marijuana by now – the topic is both fascinating, and complex. It is complex because it involves the human brain, which is the most highly organized ball of matter in the known universe and the source of a nearly unending variety of possible subjective experiences. And it is complex because marijuana is more than one thing. The weed contains over 100 distinctly identifiable different cannabinoid molecules among its over 400 different chemicals, including the fragrant and flavorful terpenes.

Basal Ganglia and Cerebellum

Complexities are also found in the motor effects of marijuana. At least three brain areas coordinate to produce our motor system. A highly specific cortical area, the convoluted layer of neuron cell bodies – gray matter – lining the surface of the brain, is wired to activate specific muscles. Wilder Penfield originally developed the distorted homunculus image spread over this area in 1937 to illustrate the amount of motor cortex dedicated to each area of the body (Figure 2.1).

Two other motor areas, each more densely populated by CB1 receptors, contribute to body movement by influencing this cortical keyboard. The first is a large collection of neurons below the surface called the basal ganglia. This area organizes memory, reward, and emotional influences into motivation. Images of achievement are generated in the basal ganglia such as "catch the ball," or "get an apple out of the refrigerator." When the

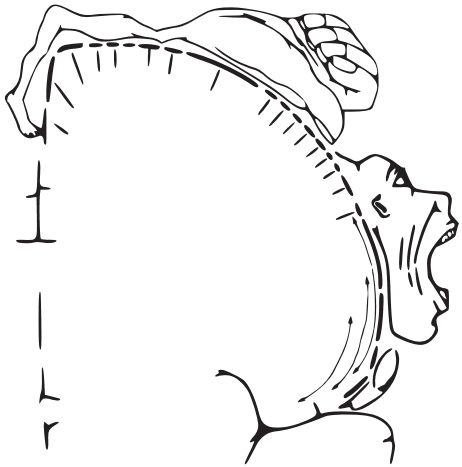

Figure 2.1 Motor homunculus. Source: Original source file Homunculus-ja.png. Translated from Image: Homunculus-de.svg by Was a bee. Author ralf@ark.in-berlin.de[22]

cloud of cannabinoids contained in marijuana smoke or vapor hits receptors in the basal ganglia, fewer images of achievement are fed into the rest of the motor system. Spontaneous motor activity is reduced. In extreme cases of "couchlock" nothing gets done. This is especially the case if marijuana with a high THC/CBD ratio is smoked. Enough THC can be given to an animal that it becomes cataplectic, or functionally paralyzed. If strongly prodded, the animal will move reluctantly, proving that no actual paralysis exists. The Urban Dictionary defines couchlock as being "so incredibly stoned that you actually become a part of the couch."[23] *Cannabis indica* strains tend to have the most sedating effects throughout the body.

Marijuana's tendency to reduce spontaneous motor activity has been used to benefit multiple sclerosis (MS) patients by decreasing their tremor.[24] There may eventually be multiple uses for cannabinoids in treating motor diseases if molecules found in nature can be modified to reduce side effects. Many people are unwilling to tolerate the psychoactive effects of marijuana in order to quell their tremor. And, unfortunately, even those MS patients who are not bothered by the psychoactive properties of marijuana have also been found to experience more rapid cognitive decline with marijuana uses.[25] While the potential medical benefits of altering our brain's cannabinoid activity will undoubtedly be far reaching, developing safe and reliably effective medications is never easy.

If, on the other hand, marijuana lower in THC/CBD ratio found in *Cannabis sativa* strains is ingested, spontaneous movement is less constrained. Images of achievement are then fed to both the motor cortex and the cerebellum, another motor area rich in CB1 receptors at the back of the brain where fine motor control is produced. Under a microscope, the cerebellum more closely resembles the highly organized structure of a microchip than any other area of the brain. The cerebellum automatically calculates and coordinates all the speeds and directions needed to accomplish images of achievement. The cerebellum is our motor computer, fine tuning signals from the motor cortex to our muscles to achieve a desired end. We run toward the fly ball, focused only on catching it, straining, and then reaching to snatch it out of the air with no more awareness of exactly how we accomplished this than most of us have of how our computer displays an email snatched out of cyberspace.

While marijuana does not affect performance on a measure of finger tapping speed, it can greatly affect perception of how long the test lasts. Infrequent marijuana users are particularly likely to overestimate the amount of time that has passed when stoned. One minute seems like several. Current theory views the cerebellum as where the brain perceives the passage of time. Raising cannabinoid tone in the cerebellum distorts estimation of time, leading people to think a minute has passed well before 60 seconds have ticked.[26]

Multiple studies have verified the negative impact of marijuana on motor coordination and reaction time. For example, when asked to trace through a virtual maze, marijuana users routinely hit the walls more frequently than non-users.[27] Reaction times are also generally lengthened, although motor responses to a Stop signal task are inconsistent, with both slower reaction time and errors of impulsive premature response[28] (which are reminiscent of the intrusive errors seen in verbal memory tests). These cerebellar effects of marijuana may be explained by the reduced activity and blood flow observed in the cerebellum in frequent users, even after 26 hours of observed abstinence.[29]

However, while the science is clear, it is sometimes more edifying to turn to the popular press. The experience of athletes tells a mixed tale. Some triathletes claim improved endurance and recovery time as a result of marijuana's positive impact on pain and inflammation, as well as putting them into "a controlled, meditational place" and élite skiers report an obvious advantage in being able to "attack the steepest lines without fear."[30] On the other hand, the same skier reported that marijuana caused him, while mountain biking, to start out confidently but eventually to misjudge his speed and ride off the trail. Scientists try to be objective, but athletes have their lives on the line. No less of an authority than FightSaga's website once concluded (prior to removing the following after beginning to run news items on the beneficial effects of marijuana for head trauma-induced chronic traumatic encephalitis):

> Most experts assert marijuana has no athletic-related performance-enhancing potential and, under its influence, is believed to:
>
> - Impair hand-eye coordination
> - Reduce reaction timing
> - Reduce motor coordination and perceptual accuracy
> - Impair concentration
> - Increase heart rate and fatigue
>
> Also, experts have stated skill impairments due to marijuana inhalation may last up to 24 to 36 hours after usage.[31]

Still, many mixed martial arts fighters continue to use marijuana, probably to reduce fear and pain.

Driving

The question of marijuana's effect on driving is important to everyone and not simply to those who use marijuana. On the face of things, driving under the influence of a psychoactive drug appears to be a bad idea. At the same time, people driving with blood levels of alcohol below the legal limit and using medically prescribed tranquilizers (e.g., diazepam or alprazolam) are deemed safe to be on the highway unless displaying evidence of impairment. Since evidence of marijuana remains in body fluids long after acute intoxication has waned, the safety and legality of marijuana users' driving is still an unsettled, and unsettling, question. Should the law enforce an absolute THC blood level limit or require evidence of impairment via a field sobriety test? Does the traditional field sobriety test used for determining alcohol intoxication adequately measure marijuana-induced impairment? And how should the law handle legitimate medical patients who have been advised to use a marijuana product as part of their treatment?

We need to look at what the data says regarding marijuana and driving to answer these questions, but the data's complexity is too great to definitively settle the matter. Basic tests of cognitive and motor skills under the influence of marijuana predict much worse driving performance than measured on obstacle courses.[32,33] An epidemiological study in France reported that drivers under the influence of alcohol were 17.8 times more likely to be responsible for a fatal accident while cannabis intoxication increased the likelihood only 1.65 times sober drivers.[34] Alcohol and marijuana have different impacts on driving. Alcohol produces an underestimation of impairment and increased speed while marijuana produces an overestimation of impairment and reduced speed (but

increased speed variability). Both slow reaction time and reduce lane stability.[35,36] The risk of driving under the influence of both, even at low doses of each, is greater than the risk of driving under the influence of either alone.[37]

The true complexity of marijuana's impact on driving was summarized by two researchers, Rebecca Hartman and Marilyn Huestis, in the following way: "Cannabis smokers share demographic characteristics similar to those of other groups with a high crash risk, including youth (ages 18–25 years), male sex, risk taking, and high drunk driving incidence."[38] In fact, youth who acknowledge real-life dangerous driving behaviors reach higher maximum speed and demonstrate more reckless driving behaviors on driving simulator tests. Young drivers with such reckless habits on the road also tend to use marijuana and to drive under its influence, which confounds the role marijuana plays in accidents.[39] Further complicating the issue is the fact that tolerance may develop in frequent smokers, with less impairment than for infrequent smokers who reach similar THC concentrations. In other words, people who are already more likely to be involved in accidents are precisely the same people who are more likely to be using marijuana.

Johnny

Johnny was a vibrant, energetic, and likable 20-year-old college student. He was in therapy primarily to work on the difficult relationship he had with his controlling father, but he had been willing to explore his relationship with marijuana as well. As a result, he had resisted the daily use his roommates practiced because of concern for its impact on short-term memory during the study week. But on weekends he enjoyed the "release" and enhancement of pleasure it offered. He left town as soon as his last class was over on Friday and raced up to the ski slopes in his black SUV where he challenged the double black diamonds, certain that being high made him a better skier. What he consciously hid from me was that his smoking started as soon as he closed the car door to begin his drive to the mountains.

When he showed up for an appointment with a scrape across his forehead that could not be hidden, I asked what happened. He told me he had rolled his SUV on the freeway headed to the mountains, and then seemed to brag that he had been lucky enough to keep the police from finding his stash. After assuring myself that he had not been badly injured, I asked, "Were you high at the time?"

"Oh yeah!" still bragging.

"Why didn't you tell me that you got stoned before driving?"

"I didn't want you to know."

"Why not? You already tell me lots of stuff about smoking."

"I knew you'd tell me not to." His tone sounded as though I had chastised him.

"Why would I tell you that?" I asked incredulously.

He hesitated. Then acknowledged, "Because it's probably not safe."

"Probably? Why would it be less safe?" By my taking this devil may care side of his ambivalence, I was hoping he would be left voicing the more rational side.

"I don't know. It feels safe enough. But the accident was my fault."

"Would you like to know what the research shows?" It was one of my favorite questions and one he had heard before. People are often more open to listening to scientific facts if they are first asked if they want to hear them. Asking for permission is an important sign of respect.

"Lay it on me, Doc," he signaled resignation to the truth.

I chose to start with facts that he would like hearing and so would not activate his defenses immediately. He agreed that he drove a little slower when stoned, maybe only 10–15 mph over the speed limit instead of his usual 25. He attributed this to normal paranoia about being stopped by the cops. He also was aware of some impairment in his attention when high, so he consciously worked to keep focused. Then, when I described the increased lane weaving and slower reaction time caused by marijuana, he quickly sat up and acknowledged the accident happened because he hadn't noticed his wandering into another car's lane and then startling when a horn blared right next to him. He overcompensated, wheels left the pavement, and he rolled into a small ditch. The other driver kept on going and so Johnny could tell the police the story he wanted them to hear – that he had fallen asleep after pulling an all-nighter to study for an important physics test. As long as I saw Johnny after that, he continued to tell me he stayed straight when driving.

William

By the time he was 16, William was so in thrall with the mystical/spiritual power of marijuana that his parents had grown very concerned about his devotion to the plant. Suddenly an avid reader of Alan Watts and Baba Ram Das's Be Here Now*, William dismissed schoolwork as trivial and irrelevant. His engineer father was scared his son was flying off the rails.*

I immediately responded positively to William's engaging, enthusiastic, but quite naïve, manner. He seemed befuddled and hurt by his family's inability to understand his new spiritual openness. I began by asking him one of my favorite open ended questions.

"What has marijuana taught you?"

"Oh man . . . everything."

"Wow . . . Can we start with the most important things?"

"I guess I'd say that it's shown me how big life is. And it's all right here, right now. When I'm stoned, I'm awed by the beauty of it all."

"Sounds like you'd been asleep and marijuana woke something up in you."

"Exactly . . . I'd been just stumbling through life without paying attention and now I know there is something more."

"Sounds exciting. How do you think marijuana has done this?"

"Does it matter?"

"In some ways no, not really. The experience you are having is real and important – part of wisdom. But in some ways studying how marijuana creates this experience for you may be important, or at least interesting."

"It's the spirit of the plant."

"Maybe. Or maybe, as some people say, it's something inherent in your brain that the plant's chemistry enhances." After valuing his experience, I felt I could begin moving its source from the bud to the brain.

"Who says that?" This is the point of inflection. William was engaged enough that he could be curious. He was the one asking for information now.

"Thousands of research scientists around the globe who have devoted their lives to understanding marijuana and the experiences people have when using it. Can I tell you some of what they have discovered about how marijuana works?"

"Yeah, I guess. I have to be here for the rest of the hour anyway."

I let William's snarky effort to save face pass without comment and skipped over the basic science for now in order to launch into the story of how electrical stimulation of the amygdala creates a sense of awe and a numinous aesthetic sense of a divine presence. From there I took him on a journey through the cannabinoid chemistry underlying the amygdala's sense of

novelty and back to the endocannabinoid system permeating his brain. This took several sessions, but he was fully engaged because I was expanding his understanding of an experience he valued. Eventually William was armed with enough scientific information that he understood there was nothing mystical contained in the plant. It was he and his brain, instead, that produced awe, wonder, and a sense of the sacred. Over time he understood Alan Watts' description of a common error among spiritual seekers – sucking the finger that points the way instead of travelling in the direction it points.

Science has now totally demystified marijuana. While hippies in the 1960s imagined they were having cosmic spiritual experiences by imbibing some numinous quality contained in the cannabis plant, they were actually experiencing heightened activity in their brain's natural endocannabinoid system. In reality, their experience resulted from a serendipitous similarity between our brain chemistry and what could merely be the cannabis plant's chemical defense against insects. Or possibly the cannabis plant developed THC to increase its chance of pollination. That part of the story still needs to be discovered.

We can now turn to what has been discovered about how frequent use of marijuana alters the endocannabinoid system beyond the period of acute intoxication. This portion of the story is highly important for health professionals and educators to understand and be able to communicate effectively. Readers may be wondering why little has been said to this point about the potential for marijuana addiction. This delay in introducing the topic is calculated. Too early discussion of addiction unnecessarily exacerbates people's defenses. The preceding information has set the scene for introducing very inconvenient truths for the proponents of marijuana use – the flies in the ointment that require everyone to know their own brain's limits. Introducing the science of receptor downregulation and its resultant cannabinoid deficiency state provides the foundation people need to understand marijuana's impact beyond acute intoxication.

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Chapter

3 Flies in the Ointment

Cannabinoid Deficiency and the Reality of Addiction

In Biblical times the ritual of anointing people with sacred oils was used as medicine to counteract dangerous spirits and demons believed to cause disease. The King James Version translated a warning in Ecclesiastes as "Dead flies cause the ointment of the apothecary to send forth a stinking savour [smell]." The phrase "a fly in the ointment" soon came to mean a small defect that spoils a desired experience – an unexpected problem that threatens to ruin something that is otherwise good. Two important flies in the ointment of marijuana need to be understood: the cannabinoid deficiency state and frank addiction.

A cannabinoid deficiency state stems from *receptor downregulation*, which refers to a reduction in the number of CB1 receptor sites that begins immediately with the introduction of exogenous stimulation, i.e., marijuana. Downregulation is an excellent example of homeostasis. As described earlier, homeostasis refers to the tendency of biologic organisms to keep their physiologic functions within prescribed limits. Negative feedback provided by the endocannabinoid system is one mechanism for regulating neuronal activity; downregulation of receptors is another. All neurons respond to sustained stimulation of their receptor sites by reducing the number of receptors. For example, if 1000 receptor sites are normally activated 50% of the time, but suddenly are all being activated 100% of the time, the neuron can return to a more normal state by getting rid of half of its receptors. This reduction, or downregulation, occurs in two phases. The first phase involves pulling receptors out of the cell membrane and into the cell's interior. This protects the receptors from being activated by neurotransmitters outside the cell. If the high stimulation continues, receptors sequestered inside the cell are gradually broken down and their amino acids recycled to build other proteins.

A subnormal number of CB1 receptors resulting from marijuana's overstimulation underlies many of the side effects of regular marijuana use. Chronic exposure to THC

reduces the number of CB1 receptors in rats from 20% to 60% in different areas of brain and a single exposure has been shown to begin downregulation in the hippocampus.[1] Daily exposure for two weeks achieved maximum downregulation of the cannabinoid receptors. But, how well does this rat research apply to humans? And what are the practical consequences of CB1 downregulation?

Postmortem examination of human brains from documented chronic marijuana users found similar degrees of downregulation of CB1 receptors, with similar regional variations.[2] Then, in 2012, the Finnish researcher Jussi Hirvonen led a team at the Molecular Imaging Branch of the U.S. National Institute of Mental Health to study the impact of chronic marijuana use on cannabinoid receptor downregulation in living humans.[3] They used positron emission tomography (PET) scans to image the brains of heavy (10 joints a day) long-term (4–37 years) marijuana users. By injecting a radioactively labeled molecule that binds to CB1 receptors, they found an average of 20% fewer CB1 receptors in cortical areas. Two additional findings were of interest. The longer an individual had used marijuana the greater was their downregulation, and four weeks of documented abstinence was enough to return the density of CB1 receptors back to normal even in heavy users. The bad news is that CB1 downregulation is real in humans. The good news is that it appears to be reversible over the course of a month.

The next logical question is whether CB1 downregulation impacts function for marijuana users. What difference does it make, if any, to have a reduction in CB1 receptors?

In essence, a *cannabinoid deficiency state* results when ongoing cannabinoid stimulation from marijuana has downregulated CB1 receptors and then marijuana use is interrupted, whether by an effort to discontinue use or simply a long night's sleep. While the normal amount of anandamide and 2-AG is synthesized from cell membranes, there are fewer presynaptic CB1 sites available to be stimulated. This leads to less of the negative feedback, circuit breaking function for which the endocannabinoid system is designed. The whole panoply of neurotransmitters that had been limited by THC's stimulation of the negative feedback loop is now released in greater abundance. The resulting cannabinoid deficiency state tends to be a mirror image of the artificial excess cannabinoid tone that underlay being high. The reduction of spontaneous motor activity generated in the basal ganglia by THC is reversed, producing motor restlessness. The impact of cannabinoid deficiency is most pronounced on the amygdala. The munchies turn into a lack of appetite, previously seen in obese patients given the cannabinoid blocker rimonabant. The suppression of painful states is reversed into a sense of general discomfort and dysphoria. At the same time, the emotional calm generated by THC is also reversed, leading to increased anxiety, stress, depressive mood (also seen with rimonabant's blockade of CB1 receptors) and even increased irritability, aggressiveness, and hostility.

The irritability and aggressiveness that can emerge during cannabinoid deficiency is a common complaint of parents when they interrupt their adolescent's marijuana use. Their child's anger is understandable on a purely psychological basis. No teen likes having a pleasure taken away when s/he feels old enough to make their own decisions. But the aggressiveness often goes beyond what is seen with other restrictions. Absence of the love drug can lead to a level of anger and hostility not seen before, as though the fight portion of the fight-or-flight response is being activated.

Signs of aggression (biting and piloerection) have been elicited in rats by using the cannabinoid antagonist SR141716 to precipitate withdrawal after pretreatment with THC or anandamide.[4,5] A laboratory study of chronic marijuana users (at least 5000 occasions) found more aggressive behavior on days three and seven of abstinence than while still using, with return to normal levels by day 28.[6] Marijuana users with a past history of aggression have also been found to have an increase in relationship aggression outside the laboratory during withdrawal.[7] The cannabinoid deficiency state is uncomfortable no matter what species experiences it. Again, the deficiency state tends to be the mirror image of being high. The latter state results from excess cannabinoid tone, while the opposite is the result of deficient cannabinoid tone. The bottom line is that good mental health requires a well-balanced endocannabinoid system.

The pleasant sense of novelty produced by cannabinoid excess is followed by its opposite – boredom – during cannabinoid deficiency. This symptom of cannabinoid deficiency is seen frequently in adolescents who use marijuana heavily. When they wake in the morning, after the THC from yesterday's marijuana has largely detached from receptors and passed out of their brain, cannabinoid stimulation is at a low ebb. The bar for experiencing novelty is now higher than normal. School is experienced as freaking boring. Even if a new idea is presented, the ability to experience a zing of novelty is blunted until school is over and there is time to light up a blunt (a cigar that has been hollowed out and then filled with marijuana). Suddenly the world regains its sparkle. Skate boarding or video games are fascinating again. Day after day can be spent on the same roller coaster, up and down each day, from boredom to interest and back to boredom repeated every 24 hours.

Of course, school is not always fascinating for everyone. There is a lot to criticize about our education system. Teenagers using marijuana heavily are not stupid and they often pinpoint the defects in our educational system to render sharp criticism. But, correct as they may be in their analyses, the fact remains that they are on an emotional, motivational, and cognitive roller coaster that is primarily reflective of alternating cannabinoid excess and deficiency.

Cannabinoid deficiency is not the same as cannabinoid addiction (or dependence – the two words are used interchangeably by people) while Cannabis Use Disorder (CUD) is the current medical term. Although cannabinoid deficiency is always part of addiction, it can exist short of full addiction. I make the distinction for two reasons. First, the cannabinoid deficiency state exists on a continuum, starting well before addiction to marijuana occurs and perhaps even for reasons completely independent of marijuana use. Psychiatry already speaks of "chemical imbalances" in the brain that lead to depression. Medications that raise serotonin levels – Selective Serotonin Reuptake Inhibitors (SSRIs) – are frequently used to treat depression, as though they are correcting a serotonin deficiency state. Therefore, we should be open to the possibility of naturally occurring cannabinoid deficiency states. This possibility is bolstered by Van Laere's work (Chapter 2) demonstrating genetic variations in CB1 availability, most pronounced in the amygdala, that produce temperamental differences. He concluded that "investigation of the functional role of the CB1 … [receptor] is warranted in pathological behavior known to be strongly related to novelty seeking [caused by low CB1 availability], such as addiction and eating disorders."[8] It may even be possible that naturally occurring cannabinoid deficiency states will someday be considered a treatable condition (unfortunately raising the likelihood that marijuana users who are devoted to their drug will

rationalize their use by claiming genetic deficiencies in their hereditary endowment of CB1 receptors). There is still much, very much, to be learned.

The second critical reason I have avoided using the word "addiction" before this point, as I do when talking to patients, is because the word is so tainted and felt to be derogatory. Many marijuana users are quite comfortable talking about experiencing a cannabinoid deficiency state but recoil from the emotionally charged label of being addicted, or dependent. One of the most important principles of motivational interviewing is to avoid activating a patient's defenses whenever possible.

This chapter began by calling receptor downregulation one of the flies in marijuana's ointment. Addiction is the other important "fly," although it is more like a leech quietly sapping the quality of life for many heavy marijuana users. Though roughly nine out of every ten people who ever try marijuana for the first time at 18 years old or older never become addicted, CUD is a reality for a relatively small but not insignificant minority. Importantly, the rate and impact of addiction is far higher for those who begin use at earlier ages. Many marijuana users, including prominent celebrities, reject the idea of marijuana addiction, calling it a threadbare scare tactic. This makes sense on two levels. They have probably not personally experienced addiction. And, if they have, they are likely reluctant to acknowledge this to themselves or others lest it call their use into question. Such is the nature of addiction to any drug.

However, there is no longer any *scientific* doubt regarding whether marijuana can be addictive. Alan Budney, at the Geisel School of Medicine at Dartmouth, is primarily responsible for organizing our thinking about the addictive properties of marijuana.[9] As a young faculty member looking for a unique topic to study, he recalled the large number of cocaine users he had seen as a postdoctoral student who were also using marijuana. Since none of his colleagues were researching marijuana, he conducted a study of interventions to promote marijuana use cessation. The surprising result was the number of patient complaints about withdrawal. A review of the literature helped him develop a checklist of potential withdrawal symptoms in 1999 that very clearly revealed marijuana withdrawal was being experienced by a good proportion of patients.[10] Coincidentally, it was in the mid-1990s that my own skepticism about marijuana addiction was challenged when I first heard patients complain of feeling anxiety when they ran out of the high potency marijuana that had recently appeared in San Francisco. Budney set about studying marijuana withdrawal to document and better characterize its symptoms and time course. In an interesting footnote to history, when Budney looked back carefully at the literature, he found laboratory studies of marijuana in the 1970s that demonstrated all the withdrawal symptoms he and his colleagues re-discovered.[11] He believes marijuana withdrawal was simply dismissed because it was not like the more serious and dramatic symptoms of alcohol, opioid, or amphetamine withdrawal.

Budney identified four lines of evidence that all converge to confirm marijuana's addictive potential.[12] The first line of evidence is the sine qua non for addiction – increased dopamine in the "reward center" (nucleus accumbens) stimulated by ingesting a psychoactive substance. A little explanation is required here.

A small collection of neurons (in Latin, the nucleus accumbens) deep in the forebrain first became famous in 1954 when James Olds, a postgraduate student at McGill University in Montreal, and Peter Milner found that rats could be rewarded by electrical stimulation to very specific areas of the brain near the hypothalamus. When rats were permitted to press the lever ad lib, they continued to the point of exhaustion, even to the

exclusion of seeking food or water.[13] Humans report a sense of pleasure when similarly stimulated, which contributed to the nucleus accumbens becoming known as the "pleasure center," or the reward center. Over the next couple of decades researchers discovered that dopamine is the chemical released in the nucleus accumbens by electrical stimulation. Dopamine was soon called the "pleasure chemical," but nothing about the brain is that simplistic.

To begin with, it is inaccurate to think of the nucleus accumbens as the "pleasure" center. The word "pleasure" is misleading and oddly anthropomorphizes the nucleus accumbens. This small collection of neurons evolved to assure that biologically important behaviors were repeated often enough for survival of both the individual and the species. Toward that end, dopamine is released in the nucleus accumbens in response to a good meal, strong exercise, and sexual activity, to name a few behaviors. All three behaviors promote survival and need to be repeated. The nucleus accumbens could more accurately be seen as a "repetition center," for that is its basic function. Dopamine release in the nucleus accumbens increases the impetus to seek whatever caused the release of dopamine.

Research has elucidated a difference between what we call "wanting" and what we call "liking," which are related to repeating and pleasure respectively.[14] A simple experiment makes the distinction. If a rat is given a choice between sugar water or water laced with cocaine, it will usually choose the sugar water. It prefers, or "likes" the sugar more. However, if rats are only given either sugar water or cocaine water and then each is removed, they will continue to press the cocaine lever far more often than they will the sugar lever. They "want" cocaine more than sugar. Rats may prefer (i.e., like) sugar water more, but they will work harder (i.e., want) the cocaine water more. This distinction is relevant to what is meant by addiction. Everyone in the addiction field has heard alcoholics and addicts say they do not even like the substance they cannot stop using.

What explains the greater wanting of the cocaine water? The answer is that all drugs of abuse cause an outpouring of dopamine into the nucleus accumbens that can be 10 times greater than any level reached by natural behaviors.[15] Animal studies have demonstrated that chronic THC produces so much dopamine in the nucleus accumbens that cellular structure is changed in the same manner seen with other addictive drugs.[16] And high-resolution MRI scans on even young adult recreational marijuana users find dose-dependent structural changes in the nucleus accumbens that are consistent with previous animal studies.[17] Not all psychoactive drugs cause a release of dopamine. Prozac alters mental life without affecting the nucleus accumbens. Antipsychotics do not release dopamine in the nucleus accumbens. But every known drug of addiction does release supranormal amounts of dopamine. This includes caffeine, tobacco, alcohol, benzodiazepines, opiates, cocaine, and methamphetamine. And it includes marijuana. This is the first line of evidence that marijuana is potentially addictive. Marijuana causes a release of dopamine above normal physiologic levels in the nucleus accumbens, the single most important criterion for addiction.

The second line of evidence involves the similarity of symptoms following precipitated withdrawal in multiple animal species. Precipitated withdrawal entails administering THC regularly for long enough to downregulate CB1 receptors and then giving a burst of the cannabinoid blocker SR141716. This procedure removes all cannabinoid stimulation far faster than merely stopping the THC. Animals are quickly thrown into complete cannabinoid deficiency. One can only imagine the intensity of "wanting"

experienced by animals that are thrust into THC withdrawal. Inner states cannot be seen directly. But animals' behavior during precipitated withdrawal is similar from species to species. Mice, rats, cats, dogs, and monkeys all become restless, irritable, tremulous, have insomnia (with similar EEG changes across species), and "wet dog shakes." It does not take a scientific mind to see that precipitated THC withdrawal is an unpleasant state. Administering THC would be an effective antidote to precipitated cannabinoid deficiency if CB1 receptors were not blocked by the SR141716. THC does quickly quell the symptoms of spontaneous withdrawal.

The third line of evidence that marijuana is potentially addictive comes from reports by regular marijuana users who choose, or are forced by circumstances, to abstain. People describe feeling irritable, restless, anxious, generally dysphoric, a little depressed, real cravings, and considerable insomnia, sometimes lasting over a month. Polysomnogram measures on nights 1, 2, 7, 8, and 13 after abrupt marijuana discontinuation in heavy users document dose-dependent (quantity and duration) declines in both total sleep and REM sleep time.[18] Poor sleep quality both prior to and after attempts to abstain from marijuana are strong predictors of early relapse.[19] The one thing that immediately erases all these symptoms is even small amounts of marijuana. These descriptions are all in users' own words and clearly resemble what is seen in animals thrown into precipitated withdrawal. Two conclusions are undeniable. Marijuana is potentially addictive for humans, especially with the stronger hybrids and THC concentrates now available. And humans are, indeed, another species of animal.

The fourth line of evidence suggested by Budney to support the conclusion that marijuana is addictive stems from its consistent parallels to other substance abuse diagnoses. Like other substance dependence disorders, CUD is a diagnosis that responds to the usual psychosocial treatments, and yet most patients have difficulty achieving and maintaining abstinence. A formal diagnosis of CUD necessarily implies the existence of an objective, observable cluster of cognitive, behavioral, and/or physiological symptoms routinely associated with excessive marijuana use. Despite these adverse consequences, people with a diagnosis of CUD generally continue their marijuana use. Among those who report near daily use, 35–40% meet the criteria established for the diagnosis of CUD.[20]

The current criteria for diagnosing CUD are generally the same as with other abusable drugs. While some clinical judgment is required to assess whether an individual's behavior is outside the range of normal, a genuine effort has been made to develop criteria that are nonjudgmental morally and ideologically. The American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorder's (DSM-5) Substance Use Disorder Work Group determined that the following observable signs are the criteria for diagnosing CUD:[21]

1. Use of cannabis for at least a one year period, with the presence of at least two of the following symptoms, accompanied by significant impairment of functioning and distress:
2. Difficulty containing use of cannabis – the drug is used in larger amounts and over a longer period than intended.
3. Repeated failed efforts to discontinue or reduce the amount of cannabis that is used.
4. An inordinate amount of time is occupied acquiring, using, or recovering from the effects of cannabis.

5. Cravings or desires to use cannabis. This can include intrusive thoughts and images, and dreams about cannabis, or olfactory perceptions of the smell of cannabis, due to preoccupation with cannabis.
6. Continued use of cannabis despite adverse consequences from its use, such as criminal charges, ultimatums of abandonment from spouse/partner/friends, and poor productivity.
7. Other important activities in life, such as work, school, hygiene, and responsibility to family and friends, are superseded by the desire to use cannabis.
8. Cannabis is used in contexts that are potentially dangerous, such as operating a motor vehicle.
9. Use of cannabis continues despite awareness of physical or psychological problems attributed to use – e.g., anergia, amotivation, chronic cough.
10. Tolerance to cannabis, as defined by progressively larger amounts of cannabis are needed to obtain the psychoactive effect experienced when use first commenced, or, noticeably reduced effect of use of the same amount of cannabis.
11. Withdrawal, defined as the typical withdrawal syndrome associated with cannabis, or cannabis or a similar substance is used to prevent withdrawal symptoms.

The work of Alan Budney remains at the core of medical thinking about criterion 11 – marijuana withdrawal.[22] The signs of withdrawal he identified include the following, with three or more beginning within several days of cessation of use required for a diagnosis of marijuana withdrawal:

- Irritability, anger, or increased aggression
- Nervousness or anxiety
- Sleep difficulty (insomnia)
- Decreased appetite or weight loss
- Restlessness
- Depressed mood
- At least one physical symptom causing significant discomfort (stomach pain, shakiness/tremors, sweating, fever, chills, headache)

Budney confirmed that the above symptoms occur in people abstaining from marijuana at home, and not only those under hospital observation.[23] Sexual differences exist, with men more likely to report insomnia and vivid dreams during periods of withdrawal, while women are more likely to report nausea and anxiety as withdrawal symptoms.[24] Budney put marijuana withdrawal into perspective by a detailed comparison with the symptoms of tobacco withdrawal (Figure 3.1).[25] In this study he asked individuals withdrawing from each to rate the intensity of a variety of specific symptoms. The graph below clearly demonstrates the similarity between withdrawal from the two drugs – tobacco and marijuana. Except for appetite and craving, all other symptoms are nearly identical in their intensity. The main difference between tobacco and marijuana withdrawal is that people have increased appetite with tobacco cessation and decreased appetite with marijuana withdrawal. This difference makes sense, since tobacco use diminishes appetite and marijuana stimulates it (i.e., the munchies). Craving is greater with tobacco, which is largely due to the relatively short time course of nicotine's stimulating effects. Increased tobacco craving may also be due to the greater frequency of lighting up a cigarette versus a joint. Smoking 20 or more cigarettes a day

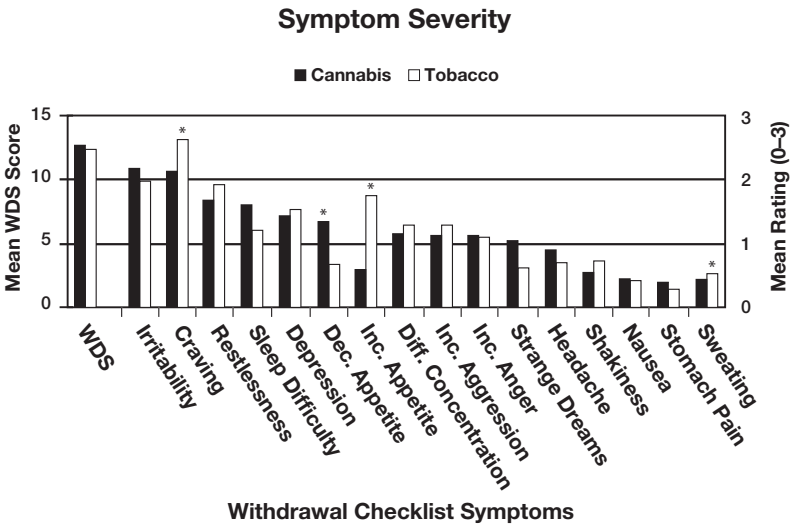

Figure 3.1 Tobacco versus marijuana withdrawal symptom severity. Source: Budney, "Comparison of cannabis and tobacco withdrawal: Severity and contribution to relapse," *Journal of Substance Abuse Treatment,* (2008); 35: 362–8.

leads to multiple associations between smoking and common daily occurrences – a telephone call, meals, driving, etc. These associations would lead to more stimulating cues throughout the day to remind people of their cigarette habit than occur with marijuana use, and more opportunities to reawaken craving by association.

The mere existence of marijuana withdrawal does not in and of itself prove it is clinically significant. To determine the practical importance of marijuana withdrawal we have to answer the following questions: How frequently does marijuana withdrawal occur? And what practical importance does it have in people's lives, if any?

Budney's research found 59% of frequent marijuana users report at least one symptom; 44% report having two or more; and 34% report three or more.[26] Among marijuana users seeking treatment for CUD, 85% report four or more withdrawal symptoms within 24 hours of abstaining.[27] Among adolescents in residential treatment for CUD, 67% described a history of marijuana withdrawal symptoms that included irritability, restlessness, depressed mood, sleep difficulty, and fatigue, or yawning.[28]

The fact that marijuana withdrawal exists does not prove its importance. The question still has to be asked, "What practical impact, if any, does withdrawal from pot have?" After all, no one addicted to marijuana is "jonesing in the gutter" and writhing with gooseflesh like the stereotypic portrayal of heroin addicts.

At least three aspects of marijuana withdrawal have been shown to be important. First, people attempting to quit complain of withdrawal symptoms, even if they do not connect their discomfort with abstaining from marijuana. Withdrawal symptoms interfere with normal daily functioning, make quitting more difficult, and frequently are relieved by restarting marijuana use.[29] Greater than 50% of people attempting to quit marijuana report that either aggression, anger, anxiety, craving, depressed mood,

difficulty concentrating, irritability, restlessness, or sleep disturbance contribute to failed quit attempts – i.e., relapse.[30]

The second practical impact of withdrawal results from the confusion between withdrawal symptoms and underlying disease. Marijuana relieves withdrawal from marijuana, whether the discomfort is identified as withdrawal symptoms or not. I have seen many marijuana users complain of difficulty sleeping when they are prevented from using their normal amount of marijuana. When insomnia continues four weeks into abstinence, many people conclude that they have an underlying sleep disorder that has been comfortably and effectively treated by marijuana. While this may be true, it may also be a premature and wrong conclusion. Insomnia lasts for up to six weeks after marijuana cessation. A similar "cause and effect" mistake is also made with anxiety. Nervousness, restlessness, and anxiety are clear signs of marijuana withdrawal. They are also the experience of suddenly having a lot of empty time on your hands, evenings needing to be organized without the distraction of marijuana, and unanswered questions about what to do with your life that may begin emerging from the fog of being "comfortably numb" (a Pink Floyd lyric many marijuana users recognize). Marijuana can be an effective "central organizing principle" for evening after evening. Returning to marijuana use relieves these anxieties and often leads to the mistaken conclusion that an anxiety disorder is being treated. Many have also told me that marijuana lifts, or at least blunts, a depressive mood, thereby giving the impression the drug is a good antidepressant. I like to respond that cocaine reliably lifts people's mood as well, but few consider it a safe or long-term alternative to exercise, better mental hygiene, or a properly chosen antidepressant medication. The strategy of increasing cannabinoid tone to treat depression is questionable at best. Good antidepressants are transparent. They lift mood without leaving people feeling drug altered. Marijuana does not pass this test for an acceptable antidepressant.

The third important practical impact of withdrawal is when significant others complain that withdrawal symptoms disrupt their partner's daily functioning. Increased irritability negatively impacts relationships with people surrounding a marijuana user. In fact, more intense aggression was observed in a home environment than in the laboratory during withdrawal, perhaps because aggression is a more intense form of irritation in response to perceived provocation by a partner.[31]

The addictive nature of marijuana has been scientifically proven beyond any reasonable doubt. The symptoms of withdrawal from marijuana and other cannabis products outlined by Alan Budney clearly meet the following scientific and clinical criteria:

- Reliability and validity of signs and symptoms
- Clear and transient time course established
- Pharmacological specificity
- Syndrome is not rare
- Clinical importance quantified

Certainty on a clinician's part that marijuana withdrawal and addiction are realities does not mean that patients are necessarily willing to accept the evidence, nor even that introducing the words "withdrawal" and "addiction" do not have the potential to destroy any possibility of meaningful dialogue. When either clinicians or patients themselves hold a moralistic view of addiction – often meaning condemnation of character weakness

attributed to addicts – it is helpful to be familiar with the genetic evidence underlying medicine's disease concept of addiction. Family histories, twin, adoption, and DNA studies by genetic epidemiologists provide substantial evidence that heredity has a significant role in the development of cannabis abuse and dependence.[32,33] Although the proportion of genetic causality for marijuana addiction is still being determined, genetic influences will undoubtedly not be the same in everyone's life. And that is precisely the point. While each individual runs some risk for marijuana addiction based solely on their genetic makeup, and not their psychology, the level of genetic risk is not the same for everyone. This genetic variability can lift the stigma from having developed withdrawal symptoms or frank CUD for many people burdened by their moralistic ideology about addiction. Clinicians help by knowing the genetic facts and embodying a nonjudgmental perspective on addiction.

Motivational interviewing (described in Chapter 12) requires a deep and genuinely nonjudgmental stance, especially during the early stages of developing a therapeutic alliance. Clinicians need to stick closely to a patient's direct experience. Understanding the power of salience in addiction helps us relate to an addict's experience. Salience is a neuroscience concept that refers to the quality of being particularly noticeable or important. The more salient an item, person, or idea is for an individual, the more it stands out relative to its surrounding context. When we are hungry, a bakery is more salient than a hardware store and we notice every bakery, restaurant, grocery, and convenience store we pass. One green dot surrounded by blue dots has more salience than the more numerous and common blue dots because the amygdala adds a zing of novelty to it. The quality of salience resides within us as the result, in the preceding two examples, of our hunger or the attraction of novelty. Salience is a quality of all addictive drugs for regular users. Once marijuana begins modifying the brain's reward system, an irrational degree of motivation adheres to anything that reminds a person of their drug. Reason can be hijacked by the emotional importance of pot, or alcohol, opiates, etc. Just as hunger sensitizes us to the slightest aroma from a distant bakery and drives us to find its source, addiction leads the mind to notice the subtlest drug cue. Addictive drugs metaphorically change the green dot in a field of blue into a blinking red dot among white ones. With excessive use, marijuana's prominence in a person's life intensifies, even against their will, when addiction takes hold of the brain's reward center. The mere thought of pot can produce a small outflow of rewarding dopamine in the nucleus accumbens, making it more likely that a joint will soon be lit. Motivation is bent in the drug's direction like iron filings around a magnet and drug-induced "wanting" melds into craving. As Hamlet said of his mother and uncle's sexual behavior, it was "As if increase of appetite had grown by what it fed on." Quite simply, marijuana addiction can change the brain in ways that create the reward and motivation to make it emotionally important to continue marijuana's use.

Understanding salience provides clinicians a platform for recognizing and acknowledging the importance of marijuana to regular users. Respecting the factual reality of this importance and not judging or fighting against it creates the experience for patients of being understood. Without first feeling understood, the door to meaningful conversation usually remains locked. When a clinician shows the willingness to understand a patient's direct experience on the patient's terms, no matter how distorted it may be by

rationalization and denial, their defensiveness may relax enough for the door to open a crack to permit more honest discussion. This opening does not require agreeing with the importance a patient places on marijuana, but rather accepting this importance for the patient. Once someone is helped to acknowledge the depth of importance marijuana holds for them, their motivations for use can be explored more fully. Although practitioners of motivational interviewing tend to describe this process in terms of the weaponless strategy of jujitsu's "going with the defense," it can also be practiced at the same depth as the psychodynamic axiom of "honoring the defense before analyzing the impulse."

Conclusion

All drug addiction and withdrawal consists of a combination of two groups of symptoms. One symptom group is unique to each drug. The other symptom group is common to all drugs. Unique symptoms follow the rule of, "For every action there is an equal and opposite reaction." In the case of marijuana, this means the characteristics of being high – relaxation, novelty, and the munchies, to name a few – are reversed during withdrawal – namely, restlessness, boredom, and loss of appetite. In the case of opiates, the calm, pain relief, and constipation of being high are reversed in withdrawal to produce agitation, pain sensitivity, and diarrhea. The methamphetamine high of energy and elevated mood is reversed in withdrawal to lethargy and depression. Marijuana's unique withdrawal symptoms are the result of downregulated CB1 receptors that produce a cannabinoid deficiency state in the same way heroin's unique opiate withdrawal results from endorphin receptor downregulation that produces an opioid deficiency state.

Withdrawal symptoms common to all drugs of addiction stem from changes in the chemistry, function, and even structure of the nucleus accumbens. When the reward center is altered by excessive dopamine, no matter which drug produces the excess, salience and motivation are attached to the experience of that drug and whatever is associated with it. Withdrawal from the drug produces a sense of urgency, both from the reward center's greed for dopamine and the discomfort of whatever symptoms are unique to that drug.

Educating both recreational and medical marijuana users about the signs of a cannabinoid deficiency state is one of the best ways to help them recognize if they are crossing an invisible line and exceeding their brain's limits. KNOW YOUR LIMITS should be a part of every marijuana education campaign and incorporated into every health professional's and educator's approach to marijuana use. The simple three-word phrase asserts that there are limits to safe marijuana use and encourages people to monitor themselves carefully. Clinicians need only remember the signs of cannabinoid deficiency (essentially the opposite of being high) to recognize when a patient has exceeded their limits enough to experience physical withdrawal from marijuana. However, it is important to remember that physical dependence is only one criterion for CUD, and is neither essential nor sufficient for the diagnosis. To oversimplify the other 10 DSM-5 criteria, whenever marijuana use causes or contributes to problems in a person's life, then an individual has a marijuana problem. Tolerance and withdrawal are not sufficient or necessary to make the diagnosis of CUD. Psychological, emotional, and cognitive changes reflecting a marijuana-altered brain are equally important signs of addiction as physical dependence.

Jason

Captain of the basketball team beginning his senior year, Jason still hoped for a scholarship to continue playing in college. He was sent to me for some marijuana education along with two of his friends when one of their parents caught them smoking weed. They were polite and attentive as I asked about their experience with pot and what they knew about how it works. When I described the cannabinoid deficiency state, Jason argued that he still found school interesting. I said I understood and thought he was smart enough that it was not necessary for him to be operating at peak levels in order to absorb his school material. However, when I described the subtle impact that a deficiency state might have on his basketball performance, he became more open and said he wanted to be as close to 100% peak performance as possible while on the court. If the ability to recognize and respond to an opponent's novel move during a game was even slightly lessened by marijuana use the day before, he wanted to take this seriously. If he were to suffer even the slightest decrement in responding to an unexpected move he had never seen before, it could easily give the man he was guarding the advantage of a half step on him. That was intolerable for Jason. He stopped using marijuana for the rest of the season. There was something he wanted even more than getting high.

Emily

A 28-year-old rape survivor struggling to establish herself professionally and socially in San Francisco, Emily was deeply ambivalent about her marijuana use. She was open to the information I offered, almost certainly because she was already feeling ill-defined doubts about her use. She hated thinking she was dependent on marijuana's balm, but repeatedly violated her promise in the morning to stop for a few days, then finding herself using again that evening. She worried she would not be able to sleep without "just a little" before going to bed. My job was to bring her ambivalence more persistently to the surface, which would intensify her discomfort, and to give more definition to the two sides of her inner conflict.

"It sounds like you sleep better with marijuana but for some reason you feel bad about using it. What do you think is wrong about using pot to get to sleep?"

"I don't want to be dependent on it."

"Why not? It works, doesn't it?"

"Yes. But I should be able to fall asleep without using a drug."

"Sure. That would be cheaper, and convenient if you ever travel out of the state. What makes it hard to get to sleep without marijuana?"

She hesitated. "I don't like talking about that?"

Suspecting she was at the edge of some trauma, I pressed lightly.

"About what? Something uncomfortable?"

"I think about the rape . . . when I woke up with my roommate's hands all over me."

"Sounds awful." I permitted my facial expression to reflect her distress.

"It is. I mean it WAS! I start getting anxious as soon as I get to my apartment each night, and it gets worse the closer I get to going to bed."

"Then you break down and have something to smoke and can relax and get to sleep. But the next morning you feel bad about breaking your promise by relying on marijuana. So, you promise yourself again not to use it that night. But the anxiety returns, as it always does, and you worry you won't get enough sleep, so you use marijuana again. Am I understanding right?"

"Yes. Only some evenings the anxiety is so bad that I have something to smoke as soon as I get home," she confesses to me sheepishly.

"Of course, because the anxiety is intolerable sometimes."

"Totally," she agreed, relieved I understood.

"I have a theory," I ventured. "Would you like to hear it?"

"A theory about what?" she asked warily.

"About a paradoxical role marijuana might be playing in your anxiety, and how we can work to reduce it a bit."

When Emily said she was interested, I outlined how even low amounts of daily marijuana downregulate receptors and leave people with a cannabinoid deficiency. She immediately identified with the symptoms of cannabinoid deficiency I outlined, adding physical restlessness and irritability to her evening anxiety. When I reduced her shame by suggesting the mild withdrawal symptoms were so disturbing because they were added on top of unresolved trauma symptoms, Emily began being comfortable labeling her discomfort as partially due to cannabinoid deficiency caused by her frequent use. She was able to recognize her brain had limits and saw how marijuana was helping her feel closer to normal by stopping withdrawal. She adopted the mantra KNOW YOUR LIMITS, which guided her toward cutting her use back to the point she no longer experienced a deficiency state when she did not use. At that point we were able to start working more effectively on her trauma symptoms.

Martin

A 35-year-old son of a hedge fund manager who lived across the country, Martin was a devoted marijuana smoker, lived in a rent free apartment provided by his father, and had never held a steady job. He saw me reluctantly after his father had researched marijuana therapists, contacted me, and demanded that his son see me weekly (for which his father paid him extra pocket money). Martin's entitlement angered his father almost as much as his being continuously high, morning to evening, 24/7. Martin despised capitalism, saw government as an evil force, and discarded all science as corrupt. While his father repeatedly exhorted me over the phone to talk some sense into his son's head, Martin spent the sessions complaining about his father's narrow-mindedness and extolling the global medical and psychological virtues of marijuana. He had no use for me as his father's lackey.

"I get it. Nothing I say has any value to you."

"Nothing."

"You have no interest in looking at whether marijuana is having any negative impact on your life."

"Nope. Don't care what you think."

"I must say I do admire your honesty . . . So, your father is wasting his money."

"I wouldn't say that. The money he's giving me for coming here isn't wasted. I use it to buy better weed. And I assume you have a use for what he pays you. He's got enough that he doesn't miss it and it gives him a sense he's helping me. Win-win all around."

"You have no doubts."

"None. Why should I?"

"I could give you dozens of reasons, but I think you take pride in ignoring them."

"Totally fucking powerless, aren't you?" he said good naturedly, with a smile of victory that comes with checkmating an opponent.

"That's the first thing we agree on."

"I've read stuff my dad sends me about the recovery racket."

I never found an entree into Martin's closed system of beliefs and eventually refused to continue seeing him, feeling it would be a lack of integrity to accept a fee for work that was having no impact. It seemed like the best lesson I had to teach was to model for his father that we are ultimately powerless to force people to change their minds.

Martin was in the 10–15% of marijuana users with whom I have been unable to forge any meaningful therapeutic relationship. At best, I hoped he would feel comfortable returning if he ever did become uncomfortable with his level of use or had trouble cutting back at some point. I include this vignette to illustrate that people who are most devoted to their drug use have firmly rationalized their behavior, often to the point of eradicating the possibility, or diminishing the importance, of being addicted. They have essentially banished any awareness or direct experience of their addiction, often by focusing on their absolute right to do as they choose or the injustices, stupidity, and evil in the world. I have no basic argument with their feelings, but wonder how all this works for them in the long run. And I content myself to wait in the wings in case a crisis in their life brings them back into my office.

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Chapter

4 Epidemiology

How Many, and Who, Use How Much Marijuana

Mark Twain popularized the saying, "There are three kinds of lies: lies, damned lies, and statistics." People distrust statistical research for at least two good reasons. First, statistics often reveal only a part of the overall picture but can be used to bias the public's perspective. An example of this, discussed in this chapter, is the lifetime prevalence of marijuana addiction in youth.

The second reason people distrust statistics is that we all lead statistically insignificant lives. Our individual experience almost never reflects overall reality accurately. We may not know a single person who uses marijuana while everyone our neighbor knows is a marijuana user. Neither of us should trust our own personal experience to judge the actual rate of marijuana use in the general public. None of us know enough people to have a reliable sample of the general public. We all live in our own small bubble. As a result, people often see no evidence personally that is consistent with epidemiological research. Some people's experience is that a whole younger generation is circling down the drain from marijuana use, while others know a star quarterback earning straight A grades who is a regular pot user and conclude that marijuana carries little or no risk for teens. It took exhausting and careful research to establish that approximately 9% of twelfth graders (in California) use marijuana 10 or more times a month.[1] While this is an established and reproducible fact, it tells us nothing about any specific individual.

Epidemiologists take a view from 30,000 feet that is unavailable to individuals and follow large population trends over decades. The University of Michigan's Monitoring the Future study, for example, surveys 50,000 8th, 10th, and 12th grade students each year across the U.S. Similarly, the National Survey on Drug Use and Health (NSDUH) annually interviews over 100,000 randomly selected individuals throughout the U.S. about use of tobacco, alcohol, and other drugs. And the EMCDDA, based in Lisbon, Portugal, provides EU members with data on European drug use and addiction.

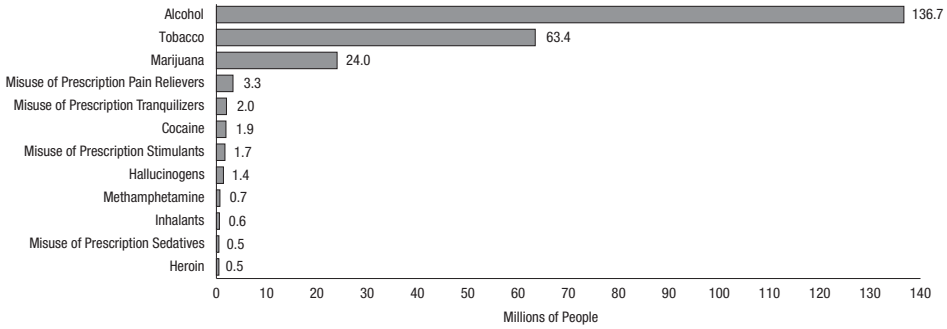

Figure 4.1 Numbers of past month drug users among US population aged 12 or older: 2016. Source: *Key substance use and mental health indicators in the United States: Results from the 2016 National Survey on Drug Use and Health* (HHS Publication No. SMA 17–5044, NSDUH Series H-52), (2017); Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration (SAMHSA), p 14. www.campusdrugprevention.gov/sites/default/files/files/2017%20NSDUH%20Findings.pdf
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www.samhsa.gov/data/sites/default/files/NSDUH-FFR1-2016/NSDUH-FFR1-2016.pdf

Epidemiological results are crowded with numbers and it is easy to get lost in the weeds. I will get out my Weedwacker and clear away the underbrush as best I can to present what we know about "How Many, and Who, Use How Much Marijuana."

In 2016, there were 270 million Americans aged 12 and older. According to the NSDUH, 28.6 million (10.6%) participated in illicit drug use during the past month. To obtain a complete picture, tobacco and alcohol consumption in the past month must also be considered. Currently, 63.4 million people use tobacco (23.5%), 84% being cigarette smokers, over half using daily. And 137 million Americans (51%) drink alcohol at least once a month, 48% of whom binge drink at least once a month. Figure 4.1 (above) shows the details of illicit drug use and places the use of all drugs in perspective.[2]

The number of past month users of alcohol and marijuana raises the important question of the degree to which recreational marijuana use and social drinking are roughly equivalent (as perhaps daily alcohol and daily marijuana users might be similar). Many social drinkers reject any comparison of their use of beer or wine as a beverage to smoking marijuana. They often deny any mind alteration with their use of alcohol (though I personally trained myself to detect the first subtle effects of alcohol after only one quarter bottle of beer). Others acknowledge an acceptable degree of relaxation from alcohol consumption while maintaining a vague but firm distinction between alcohol and pot. The following NSDUH graph (Figure 4.2) illustrates the relative amounts of alcohol consumed by different people.[3]

The official definition of binge drinking is greater than three standard drinks for women and greater than four drinks for men on a single occasion of about two hours.[4] Binge drinking does not mean a blackout, fall down full bore bender. The 61 million Americans who binge drink each month are just as intent on getting a little high as anyone who lights up a joint. I assume that most who binge drink intend to achieve an enjoyable buzz whether they are conscious of the intention with

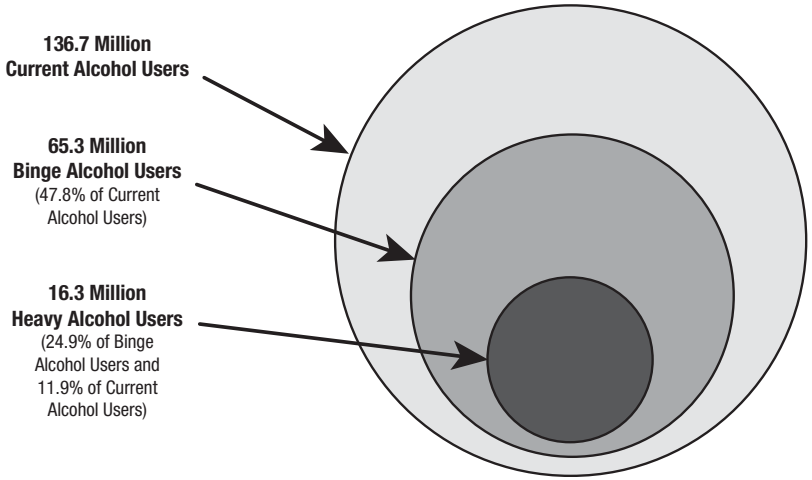

Figure 4.2 Current, binge, and heavy alcohol use among people aged 12 or older: 2016. Source: SAMHSA. *Key substance use and mental health indicators in the United States: Results from the 2016 National Survey on Drug Use and Health* (HHS Publication No. SMA 17–5044, NSDUH Series H-52), (2017); Rockville, MD: Center for Behavioral Health Statistics and Quality, SAMSHA, p 11.
www.campusdrugprevention.gov/sites/default/files/files/2017%20NSDUH%20Findings.pdf
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www.samhsa.gov/data/sites/default/files/NSDUH-FFR1-2016/NSDUH-FFR1-2016.pdf

the first drink or not. The majority of alcohol is consumed with the same purpose as marijuana (i.e., to alter consciousness) and most of us view this with little or no judgment. To be consistent, society should have the same level of judgment about, or acceptance of, non-problematic marijuana use as we generally have regarding non-problematic alcohol use. The primary differences are historical and the fact that more people using marijuana are open about their motivation to alter consciousness than people who use alcohol. Furthermore, multiple political, social, and religious ideologies, as well as entrenched economic interests, work against society's adopting a consistent perspective on the two drugs.

It is important to understand the demographics of the 24 million Americans who used marijuana during the past month because the impact of marijuana use differs for different age groups. Over the past decade, the rate of use for 12–17-year-olds has remained consistent while the rate for 18–25 stabilized for the past four years after earlier rises and the 26+ age group continues to rise. The following table and graph (Figure 4.3, Table 4.1) illustrate the relationship between age and incidence of marijuana use.[5]

The hidden factor in these numbers is the degree of impact marijuana use has on each age group. On the surface it appears that 18–25-year-olds are being the most seriously impacted, since nearly 1 in 5 young adults used marijuana at least once during the previous month while only 1 in 14 younger people (12–17 years old) used during the previous month. However, if we look at the percentage of those using who become addicted, it is immediately obvious that the younger a person begins using marijuana the greater risk he or she will be negatively impacted. The next chapter explores what

Table 4.1 Past Month Marijuana Use among People Aged 12 or Older, by Age Group: Percentages, 2002–2016.

Age	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16
≥12	6.2+	6.2+	6.1+	6.0+	6.0+	5.8+	6.1+	6.7+	6.9+	7.0+	7.3+	7.5+	8.4+	8.3+	8.9
12-17	8.2+	7.9+	7.6+	6.8	6.7	6.7	6.7	7.4+	7.4+	7.9+	7.2+	7.1	7.4+	7.0	6.5
18-25	17.3+	17.0+	16.1+	16.6+	16.3+	16.5+	16.6+	18.2+	18.5+	19.0+	18.7+	19.1+	19.6	19.8	20.8
≥26	4.0+	4.0+	4.1+	4.1+	4.2+	3.9+	4.2+	4.6+	4.8+	4.8+	5.3+	5.6+	6.6+	6.5+	7.2

+ Difference between this estimate and the 2016 estimate is statistically significant at the .05 level

Sources for Figure 4.3 and Table 4.1: SAMHSA. *Key substance use* and *mental health indicators in the United States: Results from the 2016 National Survey on Drug Use and Health* (HHS Publication No. SMA 17–5044, NSDUH Series H-52). (2017); Rockville, MD: Center for Behavioral Health Statistics and Quality, SAMHSA, p 15.
www.campusdrugprevention.gov/sites/default/files/files/2017%20NSDUH%20Findings.pdf

www.samhsa.gov/data/sites/default/files/NSDUH-FFR1-2016/NSDUH-FFR1-2016.pdf

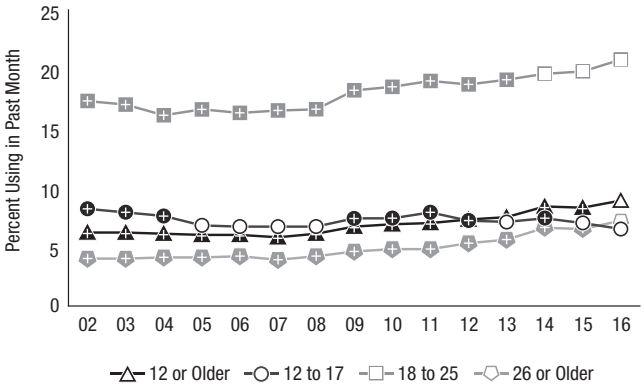

Figure 4.3 Past month marijuana use by age group: percentages.

+Difference between this estimate and the 2016 estimate is statistically significant at the 0.05 level.

researchers have discovered about the neurodevelopmental reasons for this greater impact on young adolescents.

Because statistics lump people together while every patient is an individual, I am always careful to say that marijuana is *potentially* addictive. All addiction is an interaction between agent and host. In the same way that not everyone exposed to the flu virus contracts influenza, not everyone who ever tries a potentially addictive drug necessarily becomes addicted. Factors within the host and the host's environment are as relevant to whether addiction occurs as the nature of any drug.

The concept of "conditional dependence" is useful for understanding the addictive "strength" of any drug. Conditional dependence refers to the percentage of those who ever try a drug once who eventually meet criteria for dependence, as opposed to the lifetime prevalence of addiction to that drug in the population as a whole. The very most addictive drug has always been legal – tobacco (nicotine). Thirty-two percent (32%) of everyone who ever tries tobacco becomes addicted. Only 23% of those who ever try heroin become addicted. Approximately 15.4% of those who ever try alcohol become addicted and 9% of individuals who first try marijuana at 18 years or older become addicted at some point in their lives.[6]

But, for people who first try marijuana before 18 years of age, the odds, and the speed, of addiction are markedly greater (as is also true for other addictive drugs). Unfortunately, the average age of initiating marijuana use ranges from 13.5 among Native Americans to 16.8 among Asian Americans, with other racial groups intermediate within this range.[7] Since this is the *average* age of initiation, considerable numbers begin even earlier. The following graphically illustrates the rate of dependence at different ages for those initiating marijuana use during the prior two years (Figure 4.4).[8]

While marijuana is potentially addictive at all ages, onset of use during early adolescence significantly increases the risk of addiction. Ken Winters (aptly named for a University of Minnesota researcher) demonstrated that an 11-year-old who starts using marijuana has over a 17% chance of being addicted by age 13. Starting at 12 has over a 16% chance of addiction by age 14. Starting at 16 runs almost a 13% risk of addiction by 18. Waiting until 18 to start marijuana lowers the risk of addiction by age 20

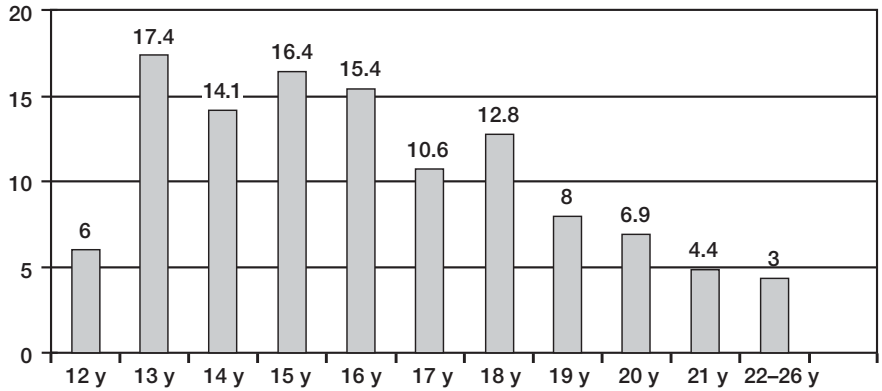

Figure 4.4 Risk of marijuana dependence in past year for different ages of onset. Source: Winters and Lee. "Likelihood of developing an alcohol and cannabis use disorder during youth: Association with recent use and age," *Drug and Alcohol Dependence,* 92 (2008); 239–47, p 242.

to about 7%. And waiting until 20 brings the risk of developing addiction within two years down to 3% at age 22.[9] The data clearly establish that *early onset of marijuana use increases the risk of addiction.*

A complexity needs to be introduced at this point. For decades the mantra within the addiction medicine field has been that addiction is a lifelong progressive disease. Physicians have watched millions of lives that ended in death or insanity from alcohol and hard drugs such as heroin and methamphetamine. Abstinence from all mind-altering drugs and a program of recovery are generally considered the only safe escape from this inevitable downward spiral. However, the work of John Horwood and his colleagues in New Zealand and Australia has shown that this dire view does not fit the facts when it comes to marijuana dependence.[10] His work also illustrates the potential for misusing statistics to support one's ideology.

Horwood followed over 1000 people in Christchurch, New Zealand, from their birth in 1972 until age 35. He found that 28% of those who started using marijuana at age 13 had met the criteria for addiction at some point by 18. By 21 years old 34% had been addicted; and a full 43% had met the criteria for CUD by age 30. This would be astoundingly bad news except for one fact – at 30 years old only 15% of those who started using marijuana at age 13 were *still* addicted during the previous year. Clearly, a 15% addiction rate at age 30 for those who started using at 13 is not good. It is highly likely that the course of life for these 15% has been significantly impacted by marijuana. *But*, Horwood's data show that 2/3 of those who developed addiction at some point after starting marijuana use at 13 were no longer addicted at 30. They had stopped or reduced their marijuana use to levels below the criteria for CUD. Their lives no longer showed the behaviors characteristic of marijuana addiction. In a similar manner, 25% of those who started marijuana at age 15 met the criteria for addiction at some point by age 30, but only 9% still used marijuana addictively during the year prior to age 30. The conclusion must be that *marijuana addiction is not inevitably a lifelong disorder.* In fact, 82% of those who have used marijuana at least 10 times stop use by age 34, the majority merely losing interest in the drug.[11,12,13]

Horwood's research illustrates that the lifetime addiction rate to marijuana is not the whole story. Most people who use marijuana addictively do so for only a limited period of time. Unfortunately, unlike tobacco, the majority of harm done by marijuana is during adolescence. Harm from tobacco addiction happens in the long run – lung cancer, emphysema, stroke, etc. Harm from marijuana addiction tends to happen more quickly – impaired school performance, delayed psychological development during the critical period of adolescence and, consequently, difficulty launching into early adulthood. Sitting on the sidelines, locked to a couch by weed, for a few adolescent years can have a profound impact on the course of an individual's life, even if the addiction to marijuana resolves later.

A close look at marijuana use among youth nationwide is provided in an annual survey by the Institute for Social Research at the University of Michigan. Called Monitoring the Future (MTF), the 2018 survey of over 43,000 students reported *lifetime* use ("ever used marijuana") by 13.9% of 8th graders, 32.6% of 10th graders and 43.6% of 12th graders.[14] In an interesting twist in the early 2000s, I participated in adding a question at a local middle school to survey perceptions of what percentage of one's peers students thought had ever used marijuana. At that time only 8% of 8th graders had ever used marijuana while they believed on average that 75% of their peers had used at least once.[15] This discrepancy by nearly an order of magnitude between actual marijuana use and perceived use continues, to lesser degrees, among European and North American university students, though it is not unique to marijuana.[16,17] Raising awareness that perception is not always reality can be a powerful, often underused, prevention tool.

MTF provides a history of waxing and waning trends in youth use of marijuana. Figure 4.5 shows the trends in *past-year* use from 1975 through 2017 for 12th graders (currently 35.9% in 2018) and since 1991 for 10th graders (currently 27.5% in 2018) and 8th graders (currently 10.5% in 2018).[18] It can be seen that lifetime statistics are not a good indicator of the true scope of current use, since 10% of 12th graders had used marijuana at least once, but not in the last year. It would be interesting to learn more about these early abstainers.

MTF found roughly the same percentage of 12th graders having ever used marijuana (45%) as having ever been drunk (46.3%) in 2015. Despite claims often heard that "everybody uses pot," this is a false justification for ignoring a teen's use. The majority (55%) of high school seniors have still never used marijuana, while only 39% have never used alcohol.

Several things are illustrated by Figure 4.5. First, the gap between 8th and 10th grades is larger than between 10th and 12th grades. Apparently, the transition from middle to high school is a prime time for many to convert from non-use to use. Prevention programs might want education about the benefits of delaying use to focus on this high-risk age group. Second, the rates of use have remained relatively stable since the mid-1990s. This seems to confirm reports that no increase in adolescent use has been stimulated by liberalization of marijuana laws and the advent of medical marijuana.[19,20] And third, prior to the mid-1990s, the annual use rate for 12th graders has been as high as 51% (1979) and as low as 22% (1992). It has generally been assumed that peaks and valleys in use are inversely related to adolescents' perception of the risk of marijuana use, elegantly illustrated by Figure 4.6.[21]

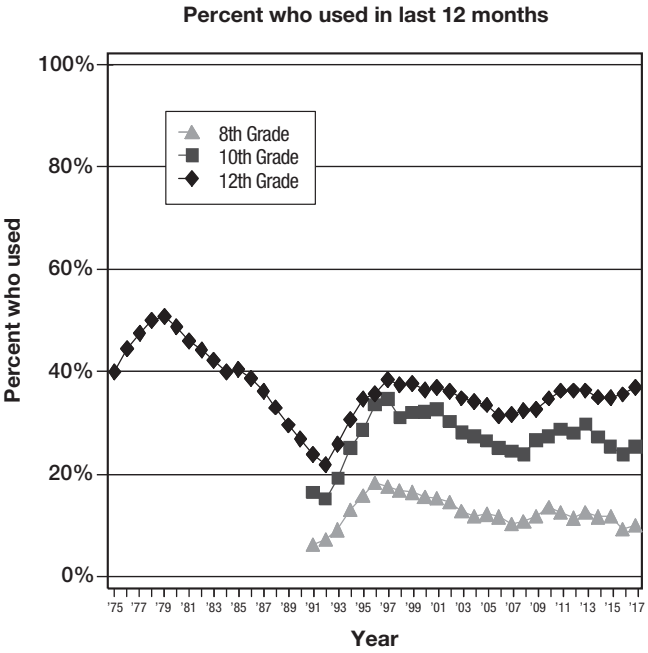

Figure 4.5 Percent marijuana use in past 12 months, grades 8, 10, and 12. Source: L. D. Johnston, R. A. Miech, P. M. O'Malley, J. G. Bachman, J. E. Schulenberg, & M. E. Patrick, Monitoring the Future national survey results on drug use: 1975–2017: Overview, key findings on adolescent drug use. (2018); Ann Arbor: Institute for Social Research, The University of Michigan.

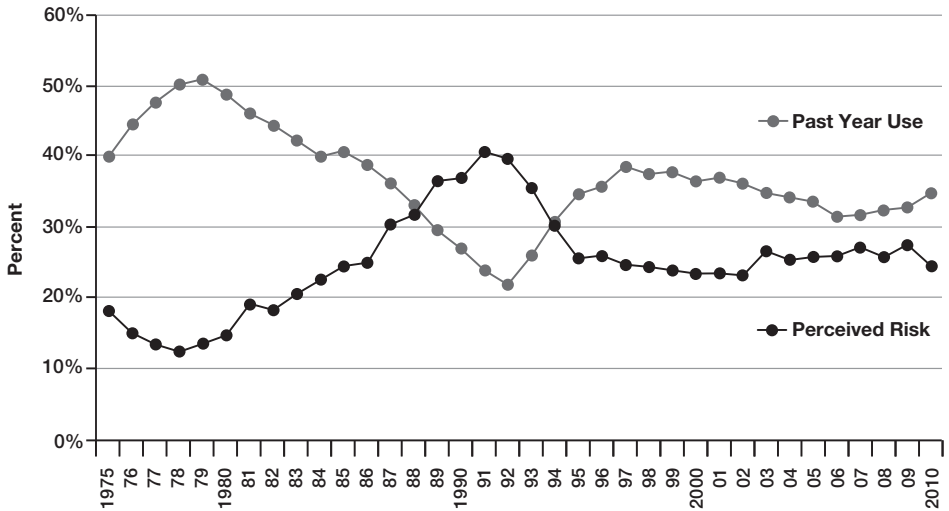

Figure 4.6 Inverse relationship between daily marijuana use and perceived risk among 12th graders. Source: Based on data from L. D. Johnston, P. M. O'Malley, J. G. Bachman, & J. E. Schulenberg, (2011). Monitoring the Future national survey results on drug use, 1975–2010: Volume I, Secondary school students. Ann Arbor: Institute for Social Research, The University of Michigan.

As the perception of safety (and desirability) of marijuana increased during the hippie 1960s and early 1970s, marijuana use rose. Then, with Ronald Reagan's presidency from 1981–1989, Nancy Reagan's "Just Say No" and Drug Abuse Resistance Education's scare campaigns, the perception of risk rose. It is impossible to tease out what proportion of the risk associated with marijuana was specifically drug related and how much was due to fear of legal consequences from the War on Drugs. It appears that when the perception of risk stabilized, the rate of use also remained consistent. It may be that a more realistic understanding of the actual level and specific character of risk involved with marijuana use penetrated into the public's awareness, but beginning in 2005 the perception of risk began a long decline without any rise in marijuana use among youth. Careful analysis of the data by Richard Miech at MTF revealed that while the significant decline in cigarette use, which is highly correlated with marijuana use, would have been expected to be paralleled by reduced marijuana use, he found a rise in the rate of non-tobacco users who did use marijuana.[22] Once the role of successful cigarette cessation efforts was factored in, the inverse relationship between perceived risk and marijuana use still held. This inverse relationship underlies the premise of this book that science-based education about the true health risks of excessive marijuana use is our most powerful prevention strategy. Miech's work is a good reminder that tobacco cessation should be integral to any efforts to prevent excessive marijuana use.

Europe is similar to the U.S. in that marijuana is the most used illicit drug by all age groups. An estimated 87.7 million European adults (aged 15–64), or 26.3%, have experimented with marijuana, often mixed with tobacco.[23] Among 15–34-year-olds, 13.9% used in the last year. European countries are far more heterogeneous than the U.S., with 3.3% of this age group in Romania and 22% in France using in the past year. As in the U.S., younger Europeans have a higher rate of past-year use – 17.7% among those aged 15–24.

The California Healthy Kids Survey provides a close up of youth in the largest state in the U.S. (over 39 million) and one of the states that most recently legalized recreational marijuana.[24] During the past month 9.5% of 9th graders and 17% of 11th graders used marijuana at least once, which is similar to the rest of the nation. It is when we look at the rate of heavy use (arbitrarily defined as 10–19 days out of each month) and regular use (20 or more days per month) that the true scope of the problem takes shape. Of 9th graders, 1% are heavy users and almost 2% are regular users, while 2% of 11th graders are heavy users and 4% are regular users. This translates into approximately 150,000 of California's nearly 2 million high school students using marijuana 10 days or more a month – 2/3 of them using 20 or more days a month.[25] With California being over 12% of the U.S. population, this leads to an estimate of approximately 1,250,000 high school students in America being too high to learn and develop normally. And these are only the teenagers who are still in school. The rate of marijuana use among school dropouts is considerably higher.

The distribution of users is perhaps a bit surprising, with twice as many regular users (20+ days per month) as heavy users (10–19 days per month), but perhaps this is in the nature of addiction. Adding to this skewing toward greater frequency of using is the fact that more frequent users also tend to use greater amounts each day, as illustrated in the following graph (Figure 4.7).[26]

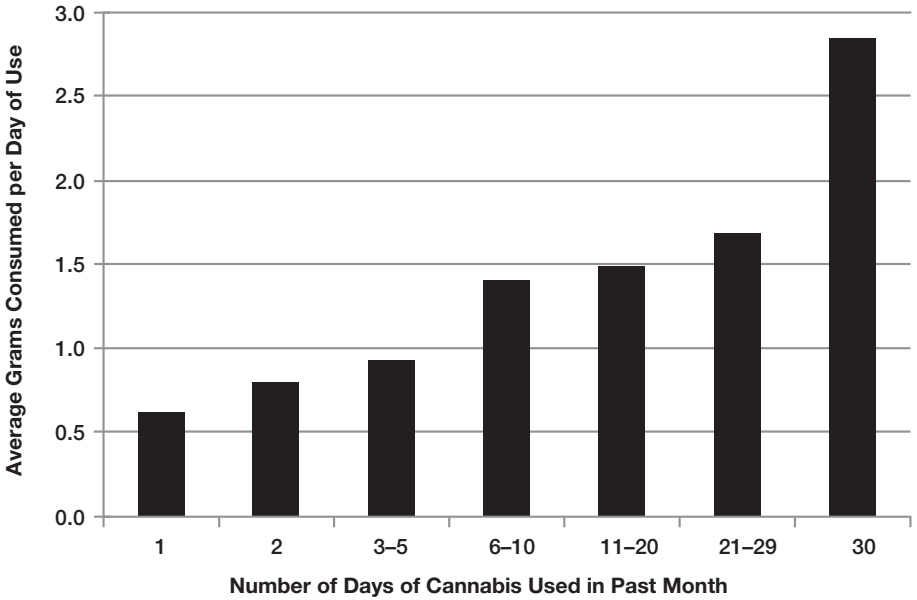

Figure 4.7 Relationship between frequency and amount of marijuana use. Source: Burns et al., "Statistics on cannabis users skew perceptions of cannabis use," *Frontiers in Psychiatry: Addictive Disorders and Behavioral Dyscontrol*, (2013); Volume 4, Article 138 (Figure 7).

Important Comorbidities

Three psychiatric conditions – Conduct Disorder (CD), Antisocial Personality Disorder (ASPD) and Attention Deficit Hyperactivity Disorder (ADHD) – are often associated with marijuana use and abuse and could potentially complicate both research into the cognitive effects of regular marijuana use and treatment of CUD. A brief overview of these conditions and the complications they introduce will be helpful at this point, with additional detail in Chapters 6.

CD is a persistent pattern of behavior during childhood or adolescence in which the basic rights of others or age appropriate societal norms are violated. Criteria for the diagnosis include aggression to people and animals, destruction of property, deceitfulness or theft, and serious violations of rules. The classic diagnosis of ASPD is only made if a history of CD existed before age 15 and symptoms increase in severity after age 18.[27] The lifetime prevalence of CD and ASPD in the U.S. is approximately 7% and 4% respectively, while the prevalence of adult antisocial behavioral syndrome without childhood CD is 12.3%.[28,29] Both CD and the adult spectrum of ASPD result from a combination of hereditary[30,31] and environmental influences and can be thought of as an unfortunate confluence of executive function deficits and a difficult temperament +/- poor parental modelling and adverse childhood events.

People with CD and ASPD are externalizing, impulsive, risk taking, novelty seeking, and more influenced by reward than punishment. These characteristics create increased vulnerability to early and frequent drug use. As a result, CD is associated with increased rates of substance initiation across all psychoactive substances. In a community sample,

the average age of marijuana initiation for adolescents with CD is 14.7 (versus 16.2 for controls) and 99% have used marijuana by early adulthood (versus 83%).[32] Over 15% of adolescents with the highest scores on CD scales are cannabis dependent at age 25.[33] When the diagnosis of CD becomes ASPD after age 18, triple the normal rate of Substance Use Disorder (SUD) is found, including cannabis, alcohol, and other drugs.[34,35,36]

The significance for our purposes of high rates of SUD in CD and ASPD is two-fold. First, unless protocols researching the effect of heavy marijuana use are designed to diagnose and eliminate subjects with these comorbidities, a significant percentage of subjects could potentially contaminate the results by importing their pre-existing cognitive function difficulties into the data. Second, disentangling the effects of marijuana use from characteristics of CD and ASPD that predate onset of marijuana use is complicated and difficult, though not impossible. Without disentangling the two influences, however, data becomes less valuable and uncertainty regarding the impact of marijuana is increased. Chapter 6 demonstrates why data on the effects of heavy marijuana use remain reliable even in the face of the complications outlined above.

Finally, a recent longitudinal study added interesting epidemiological data to our understanding of the relationship between CD and cannabis use.[37] Cannabis use in adolescence does not appear to lead to greater conduct problems. Instead, adolescents who have increasing levels of conduct problems are more likely to use cannabis and to relapse.[38] This cascading chain appears to predict CUD in emerging adulthood. In other words, CD predicts cannabis use but cannabis use itself does not predict CD.

ADHD is a neurodevelopmental disorder with a prevalence of 5% in children and adolescents[39] and of 2.5% in adults.[40] People with ADHD show a persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development. A common comorbidity of ADHD is increased rates of initiating drug use and developing SUDs.[41,42] Higher severity of ADHD symptoms in middle childhood is associated with higher rates of SUD in late adolescence and young adulthood. However, complicating the issue is the fact that early attentional problems are strongly correlated with early conduct problems and any associations between adolescent attentional problems and most SUD is mediated via conduct problems.[43.44] The only exception is cannabis abuse, which correlates directly with attentional problems.[45] Individuals with ADHD are significantly more likely to have lifetime use of cannabis than individuals without ADHD and there is no evidence that cannabis use increases the risk of developing ADHD.[46] This high prevalence of lifetime use is reflected in the finding that adults seeking treatment for CUDs have comorbid ADHD at an estimated rate of between 34% and 46%.[47]

While genetic-based hereditary overlap between ADHD and cannabis use has been reported,[48] the cognitive deficits inherent in ADHD also create vulnerability to substance use. Individuals with ADHD perform worse on verbal memory, processing speed, cognitive interference, decision-making, working memory, and response inhibition (i.e., impulsivity) compared to matched controls. Individuals with ADHD who use marijuana show no further cognitive decrements unless they began use before age 16, a phenomenon explored in detail in Chapter 6.[49]

We now turn to what science has discovered about the impacts of heavy and regular marijuana use on the brain, thinking, and psychology. As with addiction, the major impacts in all three areas occur in adolescents. Of course, all of the studies about to be

described have one drawback. They all average findings among a group of people. None of the findings, whether they involve brain structure, cognition, or psychological differences, are necessarily true for any one individual. There are always exceptions to the general rule. But 1.25 million high school students who use 10 or more days per month and adults who continue using at this level will, on average, be found to have the wide array of impacts described in the following chapters.

Melissa

After being caught and drug tested by her parents nearly every weekend for the last two months, Melissa's parents brought their 9th grader to be evaluated. Sullen, but not unwilling to talk, Melissa seemed more sad than angry. She was the youngest of three siblings, four years behind her sister, who had recently started college out of town.

"I guess you know that your parents think you are smoking marijuana too often."

"They don't understand that everyone smokes."

"All your friends?"

"Just about."

"What do you like the most about pot?"

"It's fun. Makes me happy."

"Happy is good. It does that for lots of people."

Melissa looked up at me in brief surprise, probably because she hadn't expected what sounded to her like encouragement. This opened an honest conversation about all the things she liked about pot, the camaraderie with friends, laughter, lightness, freshness. The experiences she liked gave me a hint about what might be missing from her life. She had begun using marijuana toward the end of 8th grade when her sister turned her attention toward friends she would soon be saying goodbye to as they were about to scatter to different schools. Melissa missed her sister and was able to acknowledge her sadness, but quickly denied being depressed. I agreed that my first impression was more that she was grieving a little. Normal.

"Do the other kids in your class seem happy?"

She though a few seconds, then said, "Yeah, pretty much."

"Do you think that's because they're using marijuana too?"

"Sure. Everyone does."

"Well, I may know something interesting about that. Do I have your permission?"

"For what?" Most kids are not used to grownups asking permission to speak.

"To tell you what I know that might be interesting."

"Sure." She shifted in her chair, probably anxious that I was about to put the hammer down.

"Well, it's interesting and a little confusing to me. We did an anonymous survey of eighth graders a few years ago and asked how many of their classmates they thought were using. They said about 75%."

"Sounds close, maybe a little low."

"But only 8% said they had personally used it." I could almost hear Melissa gulp. "Why do you think there was such a huge gap between perceptions and reality?" I asked this to give her the lead to help her manage any anxiety.

"Well, I think a lot more were using than admitted it. Probably scared to be honest."

"Maybe so. Maybe double the number had actually used marijuana. But you also thought more than 75% had used. So, the gap is still too big for me to understand. What do you think?"

She hesitated. "Maybe their friends had been bragging. You know. Exaggerating about having used. I don't know."

"I guess. Do people really lie about using when they actually haven't?"

"Of course."

"I know adults lie, or exaggerate, about lots of things to make themselves look good. I make this much money, I know that celebrity. You know."

"Yeah." She looked right at me and made eye contact, so I felt on solid ground with her.

"So, you said most of the people in your class are happy, but most probably have never used marijuana." I didn't finish the sentence, but wiggled my hand like there was more, hoping she would pick up the thread. After a moment she did.

"I guess I'm in the minority using pot, and you think I need it to be happy?"

"Maybe. Sometimes. Or maybe to hide from some sadness about losing your sister to college."

She looked down and was silent, then thoughtfully said, "Maybe."

Correcting perceptions with epidemiological reality can remove the excuse someone uses marijuana simply because it's the norm – everyone does. Once this rationalization is given up, it becomes more possible to explore the actual function marijuana plays in someone's life. Melissa did not stop smoking marijuana, though she did gradually cut back a lot, and she and her parents talked more openly about missing her sister.

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Chapter

5 The Impacts of Ongoing Marijuana Use on the Brain

Persistent use of marijuana has an impact on the brain, and therefore on the mind as well. Of course, people use marijuana specifically *because* it does change how the brain works acutely, but they are often not aware of the ongoing impact of marijuana on the brain/mind over time. No one sets out to produce ongoing changes in the brain, just as no one decides ahead of time that they are going to be an addict or alcoholic. And as with all drug effects, some individuals are more sensitive than others, which means that some use larger amounts without negative impacts while others are significantly impacted by lesser amounts. The consequences of ongoing marijuana use are often experienced as "happening" to an individual separate from their use, if they are noticed at all. We are now entering the realm of CUDs, meaning disorders in a person's emotional, psychological, cognitive, interpersonal, and/or social functioning as a result of the ongoing impact of regular marijuana use on brain structure and function. Because the impacts of regular marijuana use are continuous and not only when one is high, they are often not seen as induced by marijuana use. Instead, they are often seen as annoying discomforts of life or unfair treatment by others that marijuana helps soothe.

The earliest structural change seen in the brain is the downregulation of CB1 receptors described in Chapter 3. Fortunately, downregulation is largely reversible over several weeks of total abstinence. However, too frequent marijuana use does not provide sufficient time for the brain to recover its full complement of cannabinoid receptor

Special appreciation for contributions to this chapter's discussion of gray and white matter provided by T. Brumback, et al. Effects of Marijuana Use on Brain Structure and Function: Neuroimaging Findings from a Neurodevelopmental Perspective. *International Review of Neurobiology*, 2016; **129**: 33–65.

function before the next use and the impact therefore remains ongoing, as long as such use continues.

Because our endocannabinoid system regulates all other neurotransmitters, the impact of CB1 downregulation from ongoing ingestion of marijuana spreads downstream to other neurochemical systems as well. For example, if the circuit breaking function of anandamide is lessened due to downregulation of CB1 receptors, once an acute dose of marijuana wanes the presynaptic neuron releases more neurotransmitter than usual with each firing. This stimulates, or inhibits, the postsynaptic neuron more than usual, which then becomes more, or less, active than usual. This altered activity is then passed on to as many as 10,000 neurons downstream. And so on and so on, to greater and greater complexity of impact throughout the whole brain. The resultant pervasiveness of marijuana's impact means that it takes time to regain neurochemical balance throughout the brain once abstinence is initiated and upregulation is complete.

Before jumping to horrified conclusions based on the above description of THC's reverberating impact throughout the brain, it should be understood that a similar, though more narrow, process follows the prescribing of a typical antidepressant. SSRIs create a slight increase in the level of serotonin affecting downstream neurons, which are then subsequently more, or less, active than usual and this impact is passed on downstream. The majority of people who take an SSRI experience the overall impact as beneficial in a variety of ways (increased mood, decreased obsessive thoughts, lessened sense of feeling overwhelmed, etc.) despite some occasionally annoying side effects (decreased sexual desire and/or performance). One difference between SSRIs and marijuana is their highly selective nature, which is designed to focus their direct impact on the serotonin transmitter system almost exclusively, while THC directly impacts virtually all neurotransmitter systems.

Because the complexity of marijuana's impact on the brain is literally mind-boggling, most health professionals and members of the general public have little more than a vague idea of what these impacts might be beyond a "chemical imbalance." The messages regarding marijuana's impact on the brain that can be communicated to patients are threefold, and clinicians need to assess which, if any, details supporting these messages should be described to any given individual. It is useful for health professions to be familiar with the research underlying the following three messages and how to describe them to the general public:

- Brain structure suffers the greatest impact during periods of active brain development, i.e., adolescence, especially in the early pubertal period.
- The volume of gray matter and the number of synaptic connections between neurons can be reduced by marijuana use, most importantly in areas responsible for memory, emotion, and executive functions.
- The functional integrity of white matter interconnecting areas of the brain can be reduced by marijuana use.

Brain Structure

Many studies reveal that marijuana affects brain structure in multiple ways beyond the reversible downregulation of cannabinoid receptors, particularly with prenatal exposure (Chapter 9) and during puberty's explosion of neurodevelopment. Both gray and white

matter are rapidly maturing in early adolescence, which creates a critical period when disturbances from the outside are most disruptive to normal brain development.

A brief note about brain structure may be helpful. The following simple descriptions are generally within the grasp of most patients whenever further detail is desired. Gray matter consists of the closely packed bodies of brain cells. Cell bodies contain the nucleus where our chromosomal DNA is stored, mitochondria (the cell's energy factories), and the means for assembling proteins. Short extensions of cell bodies, called dendrites, are where most synapses are found for receiving input from other neurons. The surface of our brain (the cortex) is a highly folded layer of gray matter between 2–4 millimeters thick (approximately 0.1 inch). If the cortex were flattened out it would be the size of four 8 × 11 inch standard sheets of paper and contain roughly 25 billion neuron cell bodies. The hippocampus, essential for memory and learning, is one of the very oldest parts of our cortex. Some areas of gray matter, such as the basal ganglia, are found deeper within the brain, beneath the cortex.

White matter consists of the one long extension, called the axon, reaching out from each neuron cell body to connect with the dendrites of other distant neurons. Multiple axons often bundle together into what people know as "nerves" outside the brain, or "nerve tracts" when they interconnect different areas of the brain. For example, neurons in the amygdala send approximately 12 inch long axons through a circuitous route to connect with similar neurons in the amygdala on the other side of the brain. Some neurons in the spinal column extend their axons as far as an astounding 3 feet to connect with muscles in our toes – quite a prodigious feat for a one-celled animal. Layers of white fat are wrapped around axons to insulate the tiny electrical impulses racing down from the cell body at speeds up to 275 mph (430 km/h) to release neurotransmitter at distant synapses. Intricate microtubules form internal scaffolding to maintain neuronal shape and actively guide axonal growth, during fetal development.

That's the brain – gray matter and white matter – living nerve cell bodies and their axons (plus an equal number of various glial cells supporting and nourishing the neurons). Eighty to a hundred billion[1] of these single-celled organisms, woven together with almost unimaginably complex connectivity and synchronized by long nerve tracts, comprise the brain you are using right now to read this sentence and be conscious of its meaning. When you think about that, it is your brain thinking about itself, imagining its own functioning – *self* awareness!

Of course, no one begins life with a fully formed brain delivered like a new computer already loaded with the latest software updates. We all begin life as a single living cell created by the fusion of a woman's egg and a man's sperm. Early in embryonic development, neural tissue emerges and self organizes into our entire nervous system according to plans deeply embedded in our DNA. In the absence of sufficient poetic genius to express the profound mysteries of this process, I invite you simply to stand with me in awe of what God or evolution hath wrought (take your pick and I will not argue). From the moment neurons differentiate from earlier embryonic cells they embark upon a predictable developmental trajectory. Much like the construction of a house, nothing goes well if the foundation is not solid. Critical periods appear during the construction when specific tasks must be completed and damage can be done more easily. Rain can do more damage before the roof is shingled and windows installed. Wiring needs to be completed after the studs are up and before drywall is in place. In a similar way,

researchers have found that marijuana use is clearly most damaging during certain early phases of neurodevelopment.

In order to appreciate the impact of marijuana on adolescents, some understanding of the neurodevelopment experienced by teens is necessary. There are two periods of rapid brain growth in the human life cycle. The initial period of growth is during fetal development and first 18 months of extra-uterine life. This is a time of rapid multiplication of brain cells and the laying down of nerve tracts interconnecting portions of the brain. Brains are exposed to marijuana during this period primarily through maternal use prenatally and while breast feeding (Chapter 9). The second period of rapid brain development, initiated by puberty, peaks in girls at 11 years old and in boys at 12. This second period of growth involves an explosion of synaptic connections until each cell sends signals to as many as an astounding 10,000 others and receives input from up to 10,000 more. Similar to the wild springtime growth of bushes and trees, a bit of synaptic "pruning" is needed for maximum neural health. New experiences and learning strengthen some of the new synaptic connections while those that are unused disappear – a classic example of "use it or lose it." In Daniel Siegel's words, adolescent neurodevelopment is a process of "genetically governed [growth] and experientially shaped destruction."[2]

The pruning process during adolescence is important for improving the brain's efficiency. A second important neurodevelopmental process activated by puberty, called "myelination," also contributes to increasing the brain's efficiency. Myelin is a fatty sheath wrapped around neuronal axons that insulates the brain's wiring, enabling electrical impulses to flow more rapidly and accurately. Together, synaptic growth, pruning, and myelination constitute the adolescent brain development that marijuana can affect. The rate of brain maturation is highest early in adolescence and continues at a diminishing rate until the mid-twenties. As a result, the most critical period for marijuana's impact on brain development is in the early teens.

The purpose of emphasizing that the brain is constructing the most complex organization of matter in the known universe during adolescence is to emphasize the value of maintaining inherent chemical balances created by evolutionary forces. Not only is it not nice to fool with Mother Nature, but it can also have unexpected consequences.

Marijuana and Gray Matter: Neuron Cell Bodies

The volume of gray matter from ages 10–12 through early adulthood (24–25) normally decreases gradually as a result of pruning. This decrease does not occur equally throughout the brain's cortex. For example, pruning of unused neuronal connections, and thus cortical thinning, happens first in the back of the brain, where vision is processed, and then progressively moves toward frontal and temporal areas.[3,4]

While there is very little evidence of changes in *total* gray matter volume with marijuana use, smaller volumes have been found in areas richest in CB1 receptors.[5] One of the most consistent findings is smaller hippocampal volume in marijuana users relative to non-users – an average 12% smaller.[6,7,8,9] Both the amount and duration of marijuana use are implicated. The more and the longer the use, the greater the decrease in gray matter volume making up the hippocampus, our brain's basic machinery for learning and memory.

The normal relationship between learning, memory, and hippocampal volume in adults, unconfounded by changes inherent in adolescent brain development, was demonstrated in a classic study of neuroplasticity in London cab drivers.[10] Cabbies need to memorize the warren of streets, alleys, and passageways originally laid out by cow paths and other reasons long lost in antiquity. MRI studies of experienced drivers found larger than normal hippocampal volumes, with a positive relationship between length of time driving and hippocampal size.[11] Researchers then followed trainees during the three to four years it takes to learn the twisting streets of this ancient city well enough to pass the qualifying exam. Despite no differences in hippocampal volume in the beginning, those who passed the exam showed significant hippocampal enlargement and those who did not pass showed no such growth.[12] (The researchers know of no studies of London cab drivers who also use marijuana regularly; perhaps a frightening survey to ask someone to take.[13])

Given the increase in hippocampal size with intense memorization and the concept of "use it or lose it," could the reduced hippocampal volumes in heavy marijuana users be due to withdrawal from active participation in the world and thus a deficit of learning experience? Is too much "chilling" reflected in the brain, even to the point of reducing hippocampal volume? This suggestion runs up against multiple animal studies that document the direct impact of THC on the hippocampus, including reduced neuron size, 44% reduction in the number of synapses, and reduction in dendritic length.[14] In addition, the research team that first reported a 12% decrease in hippocampal volume in regular marijuana users later studied subgroups of regular users (defined as using at least twice monthly): those exposed to THC but not to CBD, those exposed to both, and former users with sustained abstinence (29 months), all subgroups determined by hair analysis.[15] Individuals using THC without CBD had an 11% reduction in hippocampal volume. When CBD was also present, hippocampal volumes were reduced by only 7%, likely due to amelioration of THC's toxicity. Sustained abstainers had a 3% reduced volume compared to controls, which did not rise to the level of statistical significance. The conclusion drawn is that CBD has a neuroprotective effect, at least in the face of THC, and recovery of harm done to the hippocampus by THC is potentially reversible. Recovery happens with sustained abstinence. As a result of the animal and human studies described above, it is likely that marijuana itself, and specifically THC, is the major culprit in altering internal hippocampal structure and reducing volume in regular users.

The high-resolution MRI of long-term heavy marijuana users by Murat Yucel (University of Melbourne) and Nadia Solowij (University of Wollongong) extended beyond the hippocampus. In addition to the 12% reduction in hippocampal volume, they also found a 7.1% reduction bilaterally in amygdala volume, the biological substrate underlying emotions, appetites, novelty, and so much more.[16] They noted how their human studies corroborated similar findings previously reported in animal literature.

As soon as one scientist makes a discovery, another comes along and finds an exception that needs explanation. It turns out that in humans with onset of marijuana use before age 16 the cortical gray matter in the frontal areas, which house higher order executive functions (e.g., judgment and abstract thinking) was thicker, which the researchers interpreted as due to a reduction in the pruning expected during this developmental period.[17] Further studies appear to identify age 16 as a point of divergence between opposite effects of marijuana use on the frontal cortex. Marijuana use onset before 16 results in thicker than normal cortex, while onset after 16 results in cortical

thinning.[18] It is possible that divergent impacts on cortical thickness between pre- and post-age 16 marijuana onset has contributed to some confusion and inconsistency in the literature regarding this topic. Either way, marijuana interacts with cortical development during adolescence and disrupts the normal trajectory of pruning. It is important to remember that bigger is not necessarily better in the brain, just as a thicker, unpruned bush may also be less healthy than one properly cared for.

Marijuana advocates and committed users are often quick to point to important caveats that need to be heeded before drawing too many conclusions from the current state of neuroimaging studies. It is true that this research is still in its early stages and data are not always consistent, most likely due to the dizzying array of variables still being sorted out. Some studies include early onset users while others focus on adult use. The marijuana used by early users is stronger today than what was used by yesterday's early users. Some marijuana is intentionally high in THC while other marijuana touts high CBD levels, which significantly alters its impact. Few studies have analyzed the THC/CBD ratio being used by research volunteers. Some research subjects have 20% fewer CB1 receptors available before ever using marijuana, especially in the amygdala, due to genetic differences.[19] Some marijuana users have experienced serious trauma, used other drugs and alcohol, have different IQs, different susceptibilities to addiction, etc., etc. The best studies attempt to control for these variables by matching age, sex, ethnicity, socio-economic status, and so on between marijuana users and controls. But research on marijuana and the humans who use it encounters all the difficulties inherent in aiming at a moving target.

Gender differences are a poorly understood and too little researched variable of potentially great importance. For example, the cortical thickness in the frontal lobes of adolescents with a history of regular marijuana use was measured after 28 days of abstinence. For reasons yet to be understood the cortex was thicker in female marijuana users than in female non-users, while it was thinner in male users compared to male non-users.[20] Thicker cortex is associated with better frontal lobe function in non-users, but poorer function in marijuana users. We do not yet understand the cause for differences between the two sexes, but it is real. An interesting example of different gender responses to marijuana is seen in the cold-water test.[21] This measure of pain threshold has men and women place their hand in 4 degrees Celsius water and time is measured until they report pain. A standard dose of marijuana produces an equal high (measured on a subjective scale), but men's pain sensitivity is reduced by marijuana while women feel no reduction in pain sensitivity. Mysteries still abound and await some clever researcher to suggest an explanation that can be tested for this gender difference.

Much more intrusive and detailed research on marijuana's impact on the brain can be conducted with animals than with humans. While rat, cat, dog, and monkey brains differ from ours, their endocannabinoid system is essentially the same. The human brain is merely a further elaboration of that found in earlier species. All mammals have their own variety of hippocampus, amygdala, and frontal cortex, but these structures appear and serve essentially the same function in all. There is nothing degrading to count ourselves among earth's grand creatures, cousins to tigers, whales, and orangutans. Animal models have clearly demonstrated that exposure to THC during adolescence, compared to exposure during adulthood, alters maturation of neural networks in the frontal cortex, hippocampus, and amygdala.[22] The impact of regular marijuana on these three areas

accounts for the majority of its long-term effects on mental functioning described in Chapters 6 and 7.

A useful strategy for dealing with incomplete or inconsistent data is to look for larger patterns that repeat across different levels of scientific inquiry, e.g., across biochemistry, physiology, anatomy, neurocognitive testing, and behavior. It is clear that very strong patterns have emerged across the different disciplines studying marijuana. I work to layer these strong patterns throughout this book in the hopes that they become progressively clearer to readers. For example, CB1 receptors are concentrated in brain areas (frontal lobes, hippocampus, and amygdala) that house the very mental functions disrupted by marijuana use (higher order executive functions, judgment, emotion, memory, and learning, respectively). Animal studies play a particularly important role in establishing the deeper layers of these cross-disciplinary patterns. Researchers can give far higher doses of THC and stronger synthetic cannabinoids than humans use. Animals can be exposed to cannabinoids prenatally and during adolescence. Dissection and detailed examination of the brain biochemical, physiological, and cellular changes document impacts by marijuana's chemistry in the same areas brain imaging demonstrates structural changes in humans. For example, rats begin downregulating CB1 receptors in their hippocampus after the first dose of THC[23] and exposure to THC during adolescence reduces the number of synapses in the rat hippocampus by 44%.[24] These findings would have been far more difficult to establish, if not impossible, without animal studies. Furthermore, an increasing number of studies of occasional marijuana users are finding evidence of subtle cognitive deficits arising from hippocampal and frontal lobe dysfunction that are more easily measured in regular marijuana users. Once these patterns are seen, non-confirming study results suggest interesting avenues for further research but do not destroy the underlying pattern. Too many results overlap on too many levels, from the molecular and microscopic to the structural and cognitive-behavioral, and point to the same conclusions to be ignored.

A consortium of Italians, led by Tiziano Rubino, published an article in 2009 that is a prime example of the cross-disciplinary approach that reveals the underlying patterns existing in marijuana research today. They treated adolescent rats with THC from 35 to 45 postnatal days and then left them undisturbed until adulthood when their spatial memory was tested. The THC pretreated rats exhibited a worse performance than controls, suggesting a deficit in spatial working memory. To correlate memory impairment to altered neural development, they performed microscopic examination of the rats' hippocampi and found that THC pretreated adolescent rats made fewer synaptic contacts in the hippocampus. Fewer neural connections led to the decrement in spatial memory as adults – from pharmacology to microstructure to behavior – all in the area where human neuroimaging finds decreased volume.[25] Marijuana research is hard work and may often involve one step backward for every two steps forward, but it is persistently pushing back the boundaries of what is unknown.

Multiple animal studies of the impact of adolescent exposure to cannabinoid stimulation confirm and expand Rubino's work. Together they speak directly to disentangling the cognitive deficits caused by marijuana from those of CD, ASPD, and ADHD. I assume that CD and ASPD do not exist in rats (although I am less sure of ADHD, since they all seem in constant motion) and thus do not import cognitive deficits into experiments on the effect of THC during adolescence on later learning. Therefore, we have strong and convincing evidence that adolescent, but

not adult, exposure to THC causes long-term impairment of a variety of learning abilities.[26,27,28,29]

White Matter: Neuronal Axons

Although each neuron sends out only one microscopically thin axon, enough axons can bundle together to form visible nerve tracts coursing through the brain beneath the outer cortical layer of gray matter. The largest bundle (the corpus callosum) consists of 200–250 million axons running in opposite directions past each other interconnecting the two sides of the brain. Einstein is reported to have had a normal sized brain but a much larger than normal corpus callosum connecting left and right sides.[30] Such efficient connectivity is likely of more importance for intelligence than absolute brain size, since healthy individuals vary greatly in brain weight.

The layers of fat wrapped around axons for insulation are an important contributor to efficiency of neural signal transmission. The competency of each cell's internal structure is also a factor contributing to efficiency. Our nerve cells have a definite, and often intricate, inner scaffolding. Neurons are not shapeless blobs like amoebae. They maintain their basic shape for a human lifetime. During early development, however, neurons must extend their axons out toward other distant neurons; and at the onset of puberty nerve cell bodies have enough plasticity to grow new dendrites and form new synapses while relinquishing old ones.

This balance between a neuron's maintaining structure and its plasticity is the product of a remarkable internal "skeleton" composed of dynamic microtubules. These microtubules are tiny straws (24 *nano*meters thick with 12 nm inner diameters) made of polymerized protein. Tubules give neurons their structure and also provide one-way transportation of nutrients, proteins, and neurotransmitters from the cell body down through the axon to distant synapses. Microtubules need to be guided during development to lengthen, reshape, and push axon growth properly. Our natural endocannabinoid system's 2-AG and CB1 receptors transiently appear in axons to guide their dynamic reshaping during fetal development. In growing neurons, phytocannabinoids not naturally produced by our body, such as THC, have been shown to displace the binding of 2-AG and disrupt the normal trajectory of microtubule growth.[31,32]

As a result of distortions in the microtubular skeleton, white matter in adolescent and adult marijuana users can lack the integrity and efficiency found in non-users. Researchers use a modified MRI technique called Diffusion Tensor Imaging (DTI) to demonstrate the effects of marijuana in white matter. DTI measures the movement of water and other molecules inside axons. When microtubules are healthy, water moves in only one direction – away from the neuronal cell body and down the axon. Multiple studies demonstrate significantly diminished coherence in the direction of water flowing through axons in marijuana users, thereby revealing lower white matter integrity. Consistent with the overall pattern of marijuana's impact, nerve tracts most impacted are found within the frontal lobes and in the portion of the corpus callosum interconnecting frontal lobes on the two sides of the brain.[33,34,35]

The significance of marijuana's impact on white matter lies in the fact that gray matter can appear normal on brain imaging even while it is functioning below normal as a result of receiving diminished input from injured axons and sending output through its own inefficient axons. An analogy would be having a perfectly good cell phone but a poor

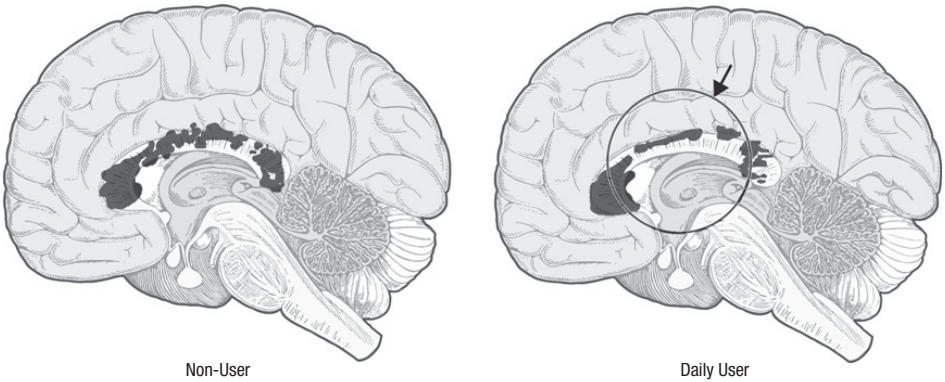

Figure 5.1 Decreased axonal integrity in the corpus callosum in marijuana users. Source: Based on Figure in Arnone, D., et al., "Corpus callosum damage in heavy marijuana use: Preliminary evidence from diffusion tensor tractography and tract-based spatial statistics," *Neuroimage* 41 (2008) 1067–74. Converted to grayscale for purposes of this publication.

cell phone network. You may be speaking clear messages, but the person at the other end of the conversation may not be receiving them accurately, and vice versa.

Disruptions in white matter integrity are revealed in images of the corpus callosum (Figure 5.1), the superhighway of axons connecting and integrating left and right brain. The image on the left is an individual with no marijuana use, while the image on the right is a regular marijuana user. Comparing the circled areas reveals areas of reduced integrity in the corpus callosum as a consequence of regular marijuana use. The axons passing through the front portion of the corpus callosum interconnect frontal areas of the brain where our executive functions are based.[36]

Of course, there is a "chicken and egg" question hanging over many of the differences in brain structure found with marijuana use. Does marijuana *cause* these changes, or do differences in brain structure lead to marijuana use? We have to be honest with ourselves here. Marijuana advocates want to believe brain differences come first, while marijuana detractors want to believe that marijuana causes brain damage. And both have data to wield in support of their position. For example, those who want to minimize the potential for harm from marijuana cite research that shows smaller frontal cortex volumes at age 12 predict initiation of marijuana use by age 16. On the other hand, a group of 16–18-year-old adolescents who reported little marijuana use at baseline but then subsequently initiated regular use were found to have decreased white matter integrity at three-year follow-up examination compared to baseline studies, which indicates that marijuana *did* cause the structural changes.[37] My own perspective on the chicken and egg, cause and effect, question is heavily influenced by corroborating animal data. While many impacts on the brain attributed to marijuana could have pre-existed use in the self-selected population of marijuana users who enroll in research studies, laboratory animals are randomized and the role of pre-existing brain differences is eliminated. We can examine a group of rat brains that have never been given THC and compare them to rat brains that have been exposed to THC. Cause and effect are clear here, and impacts similar to those seen in human marijuana users are generally found.[38] The strong pattern holds.

Michael's Parents, Irene and Paul

Over the course of his first year in high school, Michael had changed. A diligent B student and avid soccer player in the 8th grade, his grades had slipped badly, he had quit soccer, and gravitated toward new friends known to be potheads. Not bad kids – just absorbed in weed culture and reggae music. When his mother called and asked for advice on how to get Michael to agree to see me, I set up a meeting with her and her husband first.

Irene was worried about her son's inexplicable changes and focused on his not having had a haircut for over a year. She was embarrassed in front of other school mothers by the obvious changes in Michael's appearance and attitude of not caring about how others saw him. Paul, a software engineer, found his wife's concerns amusing, convinced that his son was going through the same phase he had during high school when he and his friends back in Iowa had dressed and acted like hippies for a year, to the principal's consternation.

"You see this as just a phase, almost like a prank?"

"Sure. He'll get tired and grow out of it like we did."

"And did you smoke marijuana back then too?"

"Hardly at all. Jake tried to grow some for us, but it barely got you high. Mostly we drank beer when one of us could steal a six-pack."

Irene broke in. "I hear one of Michael's new friends has a medical marijuana card for his ADHD."

I couldn't help myself and shook my head in amazement.

"That probably means Michael has access to some pretty strong marijuana. And I hear they meet at one of his friend's homes every day at 4:20, I think to get high."

I didn't take the time to explain the meaning of 4:20, but knew it derived from five students at San Rafael High School in Marin County, California who would meet at 4:20 p.m. by the campus' statue of chemist Louis Pasteur to partake. It has since morphed into a national holiday for the marijuana culture on April 20, 4/20. This probably meant Michael was pretty deeply into his new habit.

"What do you know about frequent use of strong marijuana by adolescents?"

"They're getting really high," Paul joked.

"Right. And it may be affecting their brain development. Can I show you an image of marijuana's impact on the brain?" I asked as I pulled up Figure 5.1 on my laptop showing decreased integrity of axons in the corpus callosum.

"Is that something missing in the brain?" Paul asked, suddenly serious as Irene started crying.

"Not exactly missing, but you have seen the difference in the marijuana user. This shows decreased function in the connections between the two halves of the brain – like inefficient wires between two parts of a computer that need to communicate smoothly with each other."

"Is that permanent?" Paul asked as he sat back in his chair and reached his hand over to Irene's. I had their attention in a new way.

"Good question. We don't know yet," I said slowly. No one has followed ex-marijuana users yet to see if DTI measures of axonal integrity return to normal.

"How does that affect Michael?"

"Another good question. Thank you."

We turn now from the physical changes in the brain to the alterations in brain function, especially cognition and emotion, that result in large part from these physical changes. It

is in the realm of mental functioning that the differences in brain development created by marijuana produce differences in thinking and feeling that can be experienced and observed directly. Day-to-day life is where the rubber of the mind meets the road of neurodevelopment in ways that are near enough to ongoing experience to catch people's attention, interest, and eventually their concern.

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Chapter

6

The Impacts of Ongoing Marijuana Use on the Mind: Section 1

Memory, Executive Functions, Risk Assessment, and Impulsivity

Chapter 2 reviewed the acute impact of marijuana on mental experience and functioning – being high, or stoned. This chapter emphasizes the impact of ongoing marijuana use on an individual's mind beyond the period of acute intoxication. Research has clearly shown multiple 24/7 alterations in mental functioning in the oddly named categories of heavy (10–19 times per month) and regular (20+ times per month) marijuana users, as well as with even less frequent use. This and the following chapter focus on evidence of impacts on memory, executive functions, risk assessment, impulsivity, emotion, marijuana-induced acute psychosis, schizophrenia, and pragmatic consequences found in individuals' real-world lives. The information on addiction and structural changes in the brain has laid the groundwork for a deeper understanding of the research presented in these critical chapters. Let the science speak.

Before launching into the evidence for a variety of ongoing impairments in ongoing marijuana users, anecdotal "evidence" for marijuana's ability to improve cognitive performance needs to be put into proper perspective. While non-users and very occasional users exhibit a variety of cognitive decrements with an acute dose of marijuana, daily cannabis users often experience that a dose of marijuana significantly *improves* their performance. And, indeed, research does verify improved scores on tasks of divided attention[1] and tracking (which requires sustained attention to maintain hand-eye coordination).[2] These disparate results between non-users and regular users appear to validate some people's claims of augmented powers of concentration with marijuana. However, when heavy cannabis users are challenged by a task during abstinence, they show significantly slower information processing speed compared with controls. Then, when they are retested 30 minutes after smoking marijuana, functioning normalizes.[3] So, in effect, cognitive functioning *can* improve by being high, but this is only relative to the ongoing impairment during abstinence caused by their regular heavy use. Many regular

users can accept this reality more easily when the term "cannabinoid deficiency" is substituted for addiction. The twist here is that regular users often believe they suffer from a natural cannabinoid deficiency that is corrected, and not caused, by marijuana. Such is the power of rationalization among the devoted.

A hallmark of all drug addiction is that use of the drug is needed to "feel normal," or at least closer to normal. The drug is needed to stave off the negative impacts of withdrawal – effects that begin well before more severe symptoms of obvious withdrawal appear. This phenomenon of needing a drug to feel normal was dramatically described in Robert Louis Stevenson's novel *Dr. Jekyll and Mr. Hyde*. Initially the libertine Mr. Hyde only appeared temporarily after Dr. Jekyll ingested a mysterious white powder, but eventually Hyde became the default personality *unless* the powder was taken. Only then would the normal good doctor reappear – temporarily. Addiction. It causes people to misperceive themselves and their abilities.

Memory

Studies show that marijuana impacts both "mice and men" for up to six hours after getting high, including measurable deficits in verbal memory, processing speed, and executive functioning, with the most robust effects being on short-term memory. To be more specific, THC transiently impairs recall of information presented *after*, but not before, getting high. Marijuana is particularly likely to increase intrusion errors such as "remembering" an item not on a list of words to be recalled.[4] Creative, but not accurate.

Many of these effects of acute marijuana on memory are eventually seen on an ongoing basis with regular use. Attempting to understand memory quickly becomes complex by virtue of the multiple levels of processing involved and its relationship to attention, processing speed, and learning.[5] Although memory, attention, and processing speed are three quite different mental functions, deficits of attention and slower processing speed can contribute to deficits in memory. You cannot remember what you do not pay attention to or are too slow to process. Non-users and light marijuana users show significant impairment in attention and concentration after being given marijuana and this undoubtedly contributes to lower scores on tests of memory.[6,7,8]

Learning is also an essential element in memory, just as memory is an essential element in demonstrating that learning has occurred. You cannot remember anything you have not learned and you cannot say something has been learned if there is no evidence of it being remembered. The processes involved in learning and memory include encoding a stimulus, storage or consolidation, and retrieval – or, in other words, forming a neural trace representing what is to be learned, placing that neural trace in a storage file, and then subsequently finding that file when called upon. THC at varying doses affects all three stages of this process and chronic THC exposure leaves a residue of effects.

Nadia Solowij, author of *Cannabis and Cognitive Functioning*, is one of the most published researchers on the cognitive effects of cannabis. A most thoughtful marijuana researcher, Solowij succinctly concludes that long-term heavy cannabis users perform significantly worse than shorter-term users and non-users on tests of memory and attention. These impairments endure beyond the period of intoxication and worsen with quantity, frequency, and duration of cannabis use.[9,10]

Results from the Rey Adult Verbal Learning Test (RAVLT) provide the basis for Solowij's conclusions. The RAVLT tests the ability to learn a list of 15 unrelated words (List A), which an examiner reads aloud at the rate of one per second. The task is to repeat all the words that can be remembered, in any order. The list is read and free recall tested a total of five times, which measures an individual's learning curve. Next, a second list of 15 different words (List B) is read once and recall of these new words tested. Then memory of List A is immediately retested without being read again, which tests the degree of interference by List B. After 20 minutes elapse, recall of the original List A is again retested without being read, a measure of delayed recall. Finally, a recognition test is conducted involving visual presentation of 50 words (the 30 words on both lists A and B among 20 new distracter words). Solowij's primary outcome measures from the RAVLT were total words recalled across five learning trials (numbered I–V), recall following interference (trial VI), recall following a delay (VII), and the number of words correctly recognized (VIII) – a comprehensive measure of the different aspects of memory.

Solowij first demonstrated that impairments enduring beyond the period of intoxication worsen with increasing years of regular cannabis use.[11] Her first report of RAVLT testing of marijuana users stacked the deck in favor of finding memory deficits by testing very long-term users. She tested individuals who had first tried marijuana at a mean age of 15.3 years with ongoing use (at least twice a month) commencing at age 17.5. At the time of RAVLT testing, all marijuana users had become daily, or near daily, smokers. She divided individuals seeking treatment at the median into two groups: longer-term (mean of 23.9 years) and shorter-term (mean of 10.2 years). Between 80 and 90% of both groups reported awareness of experiencing problems with memory, attention, or concentration, which they attributed to their use of marijuana. Abstinence for 12 hours was required. Long-term marijuana users performed significantly worse than shorter-term users and controls on tests of memory, with impaired learning and recall of significantly fewer words.

Next, Solowij narrowed her testing to much shorter and less frequent marijuana users, while also teasing out the possible effect of alcohol use. Marijuana users in this study first tried marijuana around age 15, with regular use commencing around age 16. They had used cannabis regularly for a mean of 2.36 years and currently used approximately 14 days per month. They self-reported abstinence for a median of 20.3 hours. Non-users and marijuana users had similar IQs. RAVLT results for marijuana users were compared to non-using controls and to alcohol only users. These shorter-term, less frequent marijuana users learned 1–2 fewer words than alcohol users and controls on all learning trials. Marijuana users remembered 6 fewer total words in trials I-V (53 versus 59 words) and an average of 1.5 fewer words on delayed recall. On the recognition trial, non-using controls and those who used alcohol only recalled all 15 words on List A, while marijuana users recognized only 14 words. Solowij points out that "adolescent cannabis users, who had used on average 2–3 times/week for 2–3 years, relative to their age-matched counterparts, had the same degree of impairment in verbal learning and memory as observed in adult cannabis users with approximately 20 years of cannabis use, but not seen in adult users of about 10 years. This speaks to the greater sensitivity of the adolescent brain."[12] Figure 6.1 presents these results visually.

Four additional graphs by Solowij drill deeper into the effect of quantity, duration, frequency, and age of onset of marijuana use. The first graph demonstrates how the total

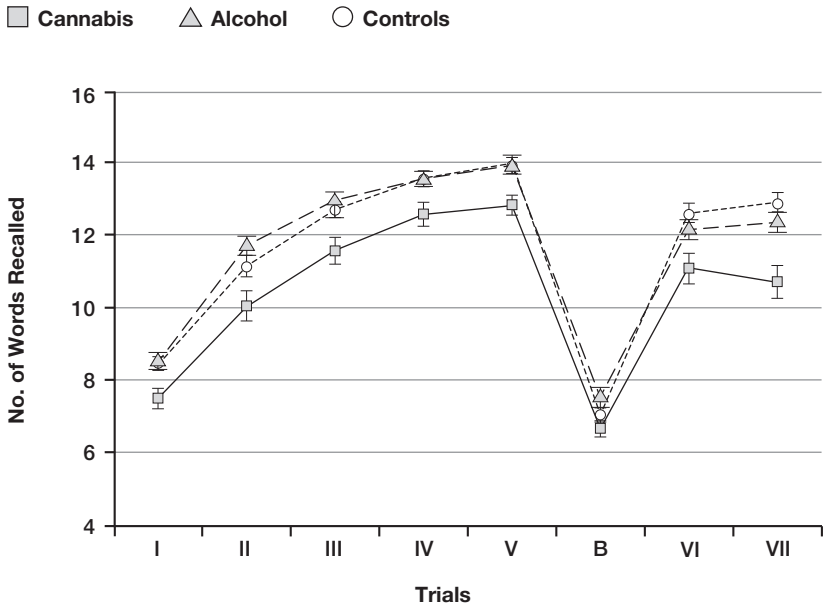


Figure 6.1 Mean words recalled on each trial of the RAVLT by cannabis users, alcohol users, and controls. Source: N. Solowij, et al., "Verbal learning and memory in adolescent cannabis users, alcohol users and non-users," *Psychopharmacology (Berl)*. 2011 Jul; 216(1):131–44.

number of words recalled worsens with increasing quantity of marijuana used (Figure 6.2).

The total number of words recalled worsens with the number of years marijuana is used (Figure 6.3).

The total number of words recalled also worsens with the frequency of marijuana use (Figure 6.4).

And the total number of words recalled worsens with earlier age of onset of marijuana use (Figure 6.5).

While the level of memory impairment in marijuana users is not *clinically* severe, (i.e., does not rise to the level of cognitive impairment warranting a diagnosis), Solowij notes that it could potentially impact school and job performance, relationships, and daily functioning. In fact, two English researchers, Fisk and Montgomery, have shown that regular marijuana use does adversely affect real-world memory function.[13] Their hypothesis was that frontal lobe-based executive functioning impairments (see following section) would account, at least in part, for everyday memory difficulties in marijuana users, but their data did not support this idea. Their laboratory testing of 21-year-olds with a 3–4 year history of regular marijuana use and 24 hours of abstinence showed no evidence of executive function deficits. However, standardized questionnaires revealed 20% worse scores among marijuana users in three measures: everyday memory, cognitive failures, and prospective memory. The Everyday Memory Questionnaire and Cognitive Failure Questionnaire ask about common memory lapses such as forgetting the location of familiar objects around the house, failing to recognize acquaintances, or forgetting

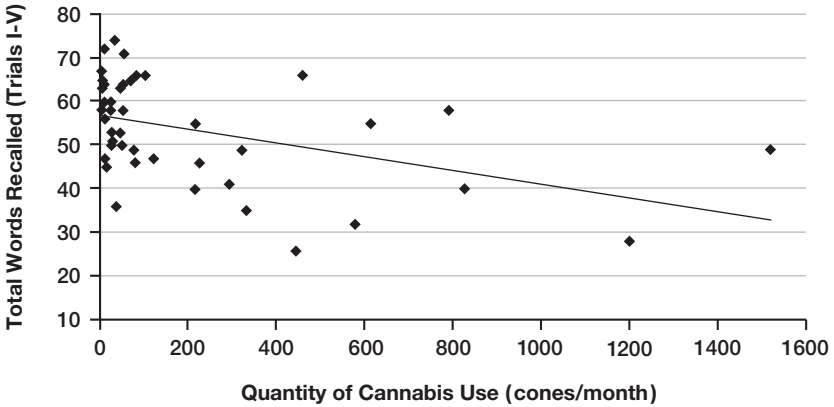


Figure 6.2 Quantity of marijuana used and impact on memory. Source: N. Solowij, et al., "Verbal learning and memory in adolescent cannabis users, alcohol users and non-users," *Psychopharmacology (Berl)*. 2011 Jul; 216(1):131–44.

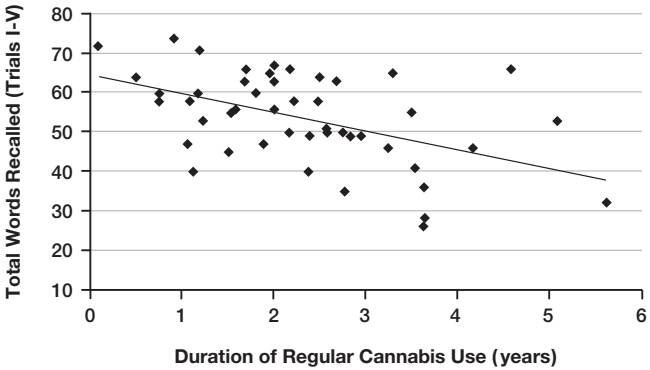


Figure 6.3 Duration of marijuana use and impact on memory. Source: N. Solowij, et al., "Verbal learning and memory in adolescent cannabis users, alcohol users and non-users," *Psychopharmacology (Berl)*. 2011 Jul; 216(1):131–44.

important events that occurred the previous day. The Prospective Memory Questionnaire asks about remembering to turn off the lights when leaving a room or remembering to attend a meeting, mail a letter, or pass on a message. In addition, the Prospective Memory Questionnaire also evaluated the use of memory aids to avoid forgetting. Because tests of everyday memory were impaired while laboratory tests of executive functions were normal, Fisk and Montgomery concluded that this was evidence either of a direct memory impairment or that the controlled laboratory environment permitted better executive function performance than what occurs in the more complex real world where the multitasking required reveals very subtle levels of cognitive deficits.

The compensatory strategies spontaneously developed by marijuana users to improve prospective memory are a natural response to any functional deficit. Research demonstrates, however, that no amount of practice can prevent decrements in basic memory functions as long as CB1 receptors remain downregulated by ongoing use of marijuana. Although the ability to "maintain" normal functioning while high may actually be the

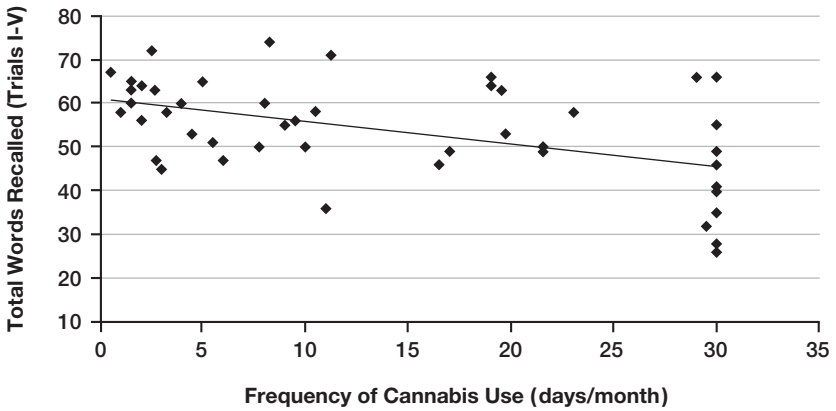


Figure 6.4 Frequency of marijuana use and impact on memory. Source: N. Solowij, et al., "Verbal learning and memory in adolescent cannabis users, alcohol users and non-users," *Psychopharmacology (Berl)*. 2011 Jul; 216 (1):131–44.

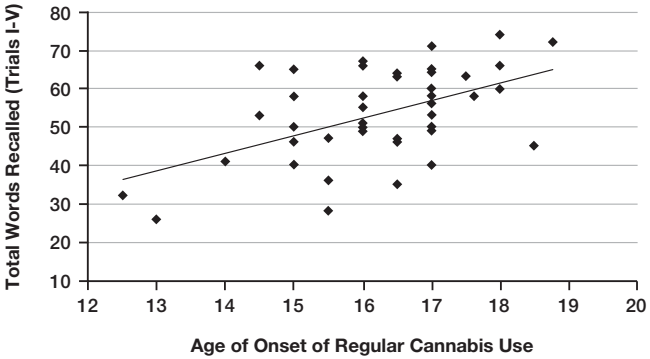


Figure 6.5 Age of onset of marijuana use and impact on memory. Source: N. Solowij, et al., "Verbal learning and memory in adolescent cannabis users, alcohol users and non-users," *Psychopharmacology (Berl)*. 2011 Jul; 216(1):131–44.

result of aborting decrements caused by withdrawal, many marijuana users consider this to be an acquired and practiced skill, i.e., the development of strategies to improve memory. In fact, spontaneous compensations by the brain have been demonstrated by Functional Magnetic Resonance Imaging (fMRI) when deficits exist in executive functions, our next topic.

In 2016, Harvard's Randi Schuster confirmed Nadia Solowij's work showing greater decrements in verbal learning in adolescents with early onset marijuana use.[14] Individuals who began using marijuana at least once a week before age 16 have reduced verbal learning and therefore reduced delayed recall compared to those who began use after their sixteenth birthday. Two years later, she reported that during the first week of abstinence 16–25-year-old regular users as a group show improvement in marijuana's negative impact on verbal learning.[15] An extension of this research should reveal the level of improvement in early users compared to late onset users as well as the degree to which abstinence-induced improvement approaches performance by non-using controls.[16]

When I was asked to speak to a local high school team about the importance of abstaining from marijuana during the football season, I was standing alone in front of a lot of big, bored guys. I learned that they had an understanding among themselves not to be stoned during games, and this already felt like a major concession by some. As I described how regular marijuana use leads to remembering fewer words on a list and to more frequent failure to remember what a person intended to do (like mail a letter), the quarterback interrupted me and ordered his teammates to listen more carefully. He pointed out that the team had over 75 plays, some with variations, and every single member of the team needed to remember their responsibility for each play. "I'm standing back there all by myself and I don't want my ass handed to me because one of you is smoking too much dope to remember what you're supposed to do," he commanded. I am pretty sure most of the guys listened to their popular quarterback a lot more than they listened to me, and he told me later he would not have been convinced my opinion was worth paying attention to without the science I provided.

Executive Functions

Although previous discussions of cognitive abilities introduced the concept of "executive functions," it will now be helpful to explain this important concept further. Our executive functions are a set of neurologically-based skills that permit self-regulation and behavior required to achieve a goal. The following provides a more complete list and description of the higher order cognitive functions produced by maturation of the frontal lobes:

- *Attention*: Selectively focusing on one aspect of the environment or internal mental content while ignoring others
- *Concentration*: Maintaining intense mental focus over time
- *Decision-Making*: Selecting a course of action among several alternatives with a goal in mind
- *Impulse Control*: Imposing restraint on behavior
- *Emotional Regulation*: Achieving a balance between emotional flow and restraint, the latter often by cognitive thought processes
- *Set Shifting*: Mental flexibility to consider new perspectives in the face of new information
- *Self-Monitoring*: The ability to evaluate one's own performance
- *Prioritization*: Differentiating relative importance of goals
- *Planning*: Breaking a task into manageable steps
- *Sequencing*: Maintaining proper order of steps to achieve a goal
- *Abstract Thinking*: Thinking in terms of concepts and general principles
- *Judgment*: Forming an opinion by discernment, comparison, accurate estimation of immediate and future consequences.

Executive functions permit us to manipulate ideas mentally, pause to think before acting, meet unanticipated challenges flexibly, resist temptations, assess risk, and stay focused.[17] Our executive functions are not discrete and easily enumerated like the fingers on our hands. Rather, they are overlapping and generally defined by the neuropsychological tests developed to measure them. Our executive functions are essentially what people mean by "intelligence."

There is abundant evidence that our executive functions are diminished both by acute ingestion and ongoing use of marijuana. The persisting impact of chronic marijuana use on memory may be the most robust finding, but its impact on executive functions is probably more important. Even after attention and memory are largely restored with abstinence, marijuana's impact can continue impairing executive functions for another three weeks. The most enduring and detectable deficits occur in decision-making, concept formation, and planning.[18]

Neuropsychologists have developed a wide array of testing procedures to measure the basic elements of our executive functions. Some of these tests are quite simplistic and others are almost Machiavellian. Neuropsychological tests could be compared to the Punt, Pass, and Kick competition sponsored by the National Football League (NFL). There is no guarantee that winners will ever be good football players, but those who do poorly are quite unlikely to become stars of the NFL. In a similar way, neuropsychological testing assesses an individual's basic cognitive capacities, but not whether these abilities will ever be put to good use. Ineffective strategies for confronting life's challenges develop during periods of marijuana-induced impairment. These less effective strategies can continue to hold sway after abstinence restores the full range of executive function. In other words, a stoner lifestyle and worldview can continue to affect an individual's identity well after marijuana is no longer a part of his or her life. The work needed to mature one's use of restored executive functions is part of what is referred to as "recovery."

Before looking in greater detail at specific decrements in executive functioning caused by regular marijuana use, it is important to recall that these higher order cognitive capabilities reside primarily in the frontal lobes, where marijuana reduces CB1 receptors by 20% and interferes with efficient axon connections both between portions of each frontal lobe and between frontal lobes in the two hemispheres. The impact of ongoing marijuana use on adolescent frontal lobes can be permanent as a result of interfering with gray matter pruning and diminishing the integrity of axon connections.

Because interference with structural neurodevelopment occurs during adolescence, placing this age group at the highest risk of being harmed, I will first focus on impairments in executive functions at these early ages. I begin with the work of Krista Lisdahl Medina (now at the University of Wisconsin while still part of a highly productive research team at University of California San Diego). Medina evaluated executive functions in adolescent marijuana users (age 16–18) after a month of monitored abstinence. Over half had used for about three years, meaning their onset of use was early – between ages 13 and 15. The number of lifetime uses of marijuana ranged between 60 and 1800 times. Half had three or more symptoms of dependence. Even after a month of abstinence, adolescent marijuana users had subtle deficits in psychomotor speed, complex attention, verbal story memory, and planning/sequencing, compared to a matched non-using control group. Her findings are illustrated in Figure 6.6.[19]

Medina measured complex attention with the Digit Symbol test (described in Chapter 2), which gives a measure of processing speed, memory, and complex attention.

Sequencing is measured by a "connect the dots" test called Trail Making. After making separate trails, one connecting numbers (1-2-3 . . .) and the other connecting letters (A-B-C . . .), a third trail is made alternating between numbers and letters (1-A-2-B-3-C . . .), as shown in Figure 6.7.

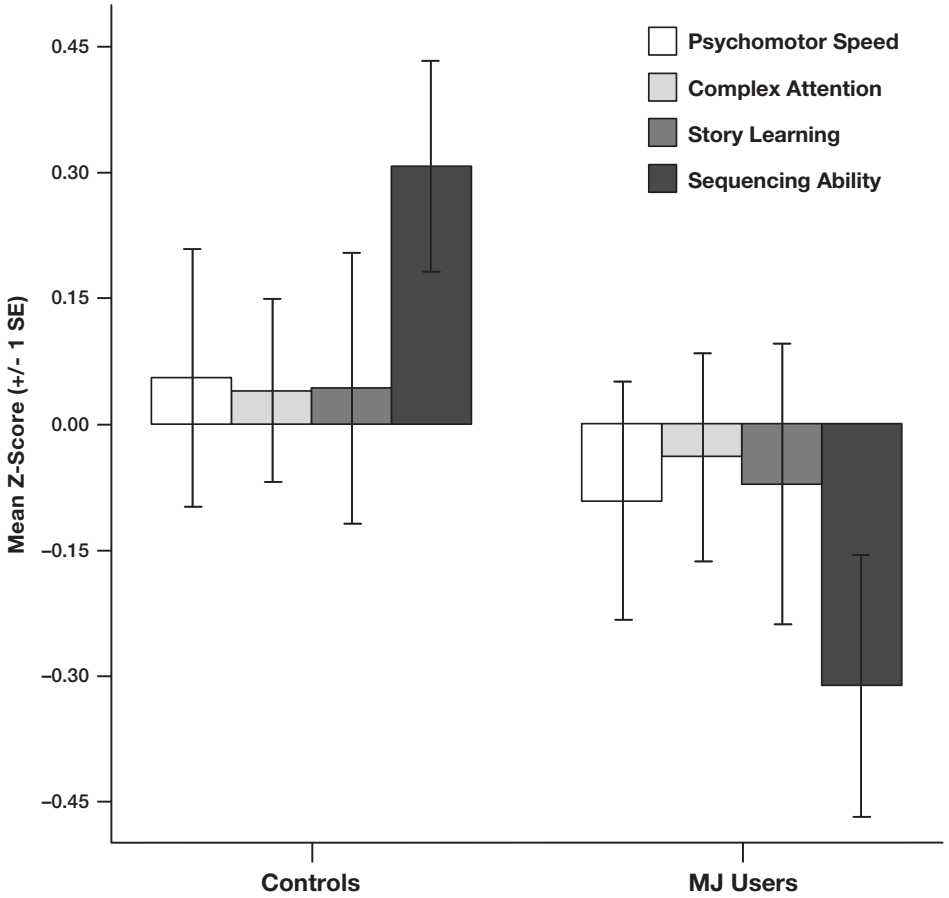


Figure 6.6 Executive functions in adolescents after one month abstention. Source: PowerPoint image by Krista Medina Lisdahl based on data in: Medina et al., "Neuropsychological functioning in adolescent marijuana users: Subtle deficits detectable after a month of abstinence," *Journal of the International Neuropsychological Society* (2007), 13, 807–20.

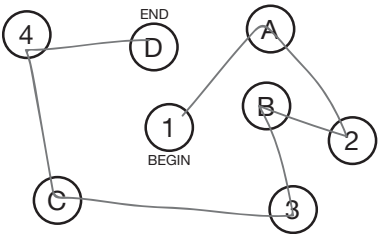


Figure 6.7 Trails A and B.

While these tests look quite basic, so are the skills of punting, passing, and kicking; but in the hands of a skilled evaluator, important patterns can be seen. Previous to Medina's evaluating executive functions specifically in adolescents after 23 days of abstinence, researchers had reported no measurable deficits in attention, short-term

memory, and psychomotor speed in adults after similar lengths of abstinence. One prominent study of lingering cognitive deficits in abstinent adults found "Some cognitive deficits appear detectable at least 7 days after heavy cannabis use but appear reversible and related to recent cannabis exposure rather than irreversible and related to cumulative lifetime use."[20] In contradistinction, Medina concluded that marijuana use during adolescence negatively impacts neurodevelopment, thereby resulting in more persistent cognitive consequences compared with use during adulthood. She noted that her findings were consistent with cellular changes seen in mice, rats, and primates after chronic marijuana exposure, especially in frontal and hippocampal areas. Her work further reinforces the pattern of marijuana's multiple impacts on brain structure during adolescent neurodevelopment that lead to decreased executive functions.

Science is a human enterprise, with graduate students striving under their professor's watchful eye to prove themselves equal to the tasks of high-quality research. Within research teams, individuals often piggyback their own experiments onto colleagues' work and then can be named first author on the paper reporting their results. Three years after Medina's publication, one of her co-authors, Karen Hanson, published results of work performed simultaneously on some of the same individuals Medina studied. Hanson administered a brief battery of tests on three occasions – after three days, two weeks, and three weeks of marijuana abstinence – to follow in greater detail the most robust findings emerging from Medina's research. This allowed Hanson to measure the course of improvement in the most impaired executive functions. Word list learning improved after two weeks of abstinence and verbal working memory after three weeks, but attention deficits persisted.[21] These results again implicate hippocampal and frontal cortex abnormalities during early abstinence in adolescents. One important implication of these data is that intermittent marijuana use during adolescence (i.e., every other week) may still be capable of producing ongoing executive function impairment.

The scene shifts to Brazil at this point where a team of scientists led by Maria Fontes studied differences in executive functions between adolescents who started using marijuana before the age of 15 and those who started later. Early onset produced significantly poorer sustained attention, impulse control, and cognitive functioning compared to later onset of marijuana use.[22] Fontes administered a battery of standard neuropsychological tests focused on frontal lobe function to measure the capacity for conceptualization, mental flexibility, sensitivity to interference, and inhibitory control. Two tests also estimated IQ. In addition, two tests of complex and integrated executive function were administered – the Wisconsin Card Sort and the Stroop test, both of which require some detailed description for readers to understand the problems created by early onset of marijuana use.

The Wisconsin Card Sort requires individuals to sort a set of cards, each of which contains one of four symbols (e.g., square, circle, etc.) printed in different colors. Each card can have from one to three copies of the same symbol. No instructions are given for how cards are to be sorted, whether by symbol, color, or number of symbols on each card. After an individual decides to sort cards on the basis of the symbol it contains, the number of symbols, or the color, the test administrator reveals whether their guess is correct, or not (Figure 6.8).

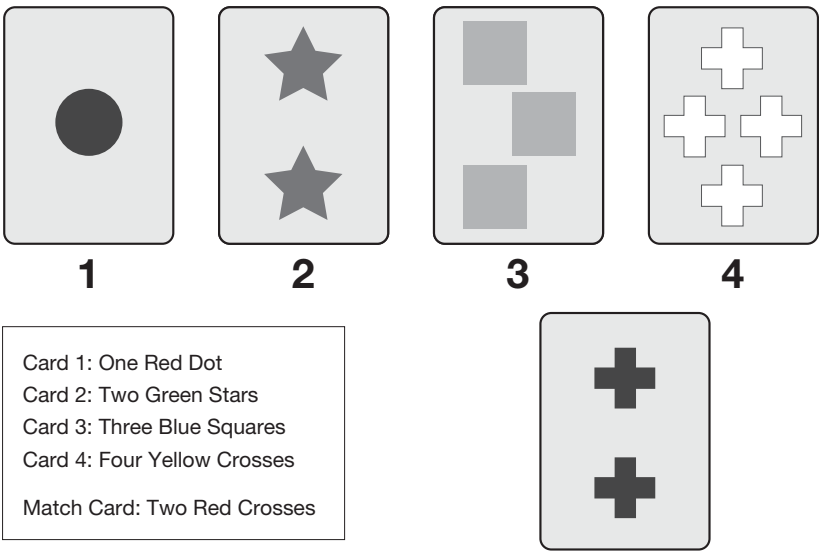
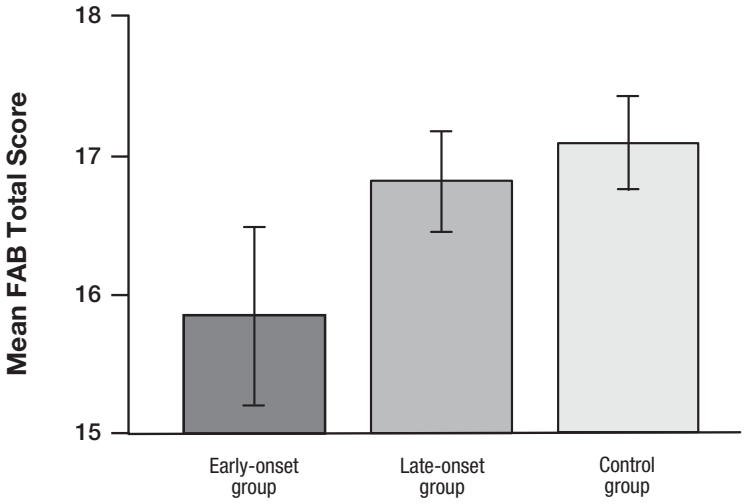


Figure 6.8 Wisconsin Card Sort. Source: Screenshot from the PEBLcomputerized version of the Wisconsin Card Sort (converted to grayscale for purposes of this publication).
https://en.wikipedia.org/wiki/Wisconsin_Card_Sorting_Test

The task confronting test takers is to develop hypotheses for how to sort the cards and then to test their hypotheses by trial and error until they discover the correct answer. Then, after a standard number of correctly sorted trials, the administrator arbitrarily changes the correct sorting strategy without informing the test taker. The task now becomes one of mental flexibility. Close attention is paid to the number of times an individual returns to the old, now incorrect, strategy – a measure of perseveration. Scores on the Wisconsin Card Sort measure an individual's capacity for planning, conceptualization, and mental flexibility. It is easy to see how scoring well on this test might predict good problem-solving skills in the real world.

The Stroop test investigates a narrower aspect of executive functioning – the ability to suppress irrelevant stimuli interfering with a desired response. First, it is ascertained that test subjects are not color blind and can read the names of simple colors printed in black ink. Then the names of colors (e.g., "blue," "green," or "red") are printed in colors that differ from the names. For example, the word "red" is printed in blue ink. Correctly naming the color blue in which the name "red" is printed is more prone to error than when several Xs are printed in blue. The verbal meaning of the word "red" interferes with naming the blue color in which it is printed. The Stroop test is a measure of how well the impulsive intrusion of one's divided attention can be suppressed. It is likely that poor performance on the Stroop would correlate with the increased interference Solowij found that the second list of 15 words had on the RAVLT scores of marijuana users.

Evaluating executive functions in early onset regular marijuana users separately from late onset users and non-using controls unequivocally demonstrates the greater neurotoxicity of marijuana below the age of 15. Figure 6.9 illustrates poor performance on the Frontal Assessment Battery as a whole by late onset users and even poorer performance by early onset users compared to non-using controls.



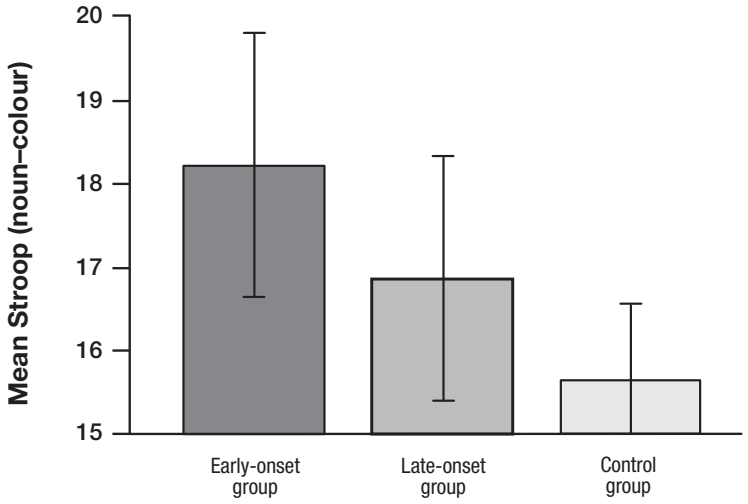
Frontal Assessment Battery (FAB) total score in early-onset, late-onset, and control groups.
Error bars: 95% confidence intervals.

Figure 6.9 Impact of marijuana on executive function. Source: M. A. Fontes et al., "Cannabis use before age 15 and subsequent executive functioning," *Br J Psychiatry*, 2011, 198: 442–7; DOI: 10.1192/bjp.bp.110.077479. Correspondence: Maria Alice Fontes, Rua Dr José Gustavo Busch, 155–121B Morumbi, São Paulo SP Brazil, ZIP 05705–190.

Performance on the Stroop test of interference, measured in terms of the number of intrusive errors and increased time required to respond, also illustrates the poorer performance of early regular marijuana users, who are less able to filter out unwanted stimuli (Figure 6.10).

Results on the Wisconsin Card Sort, which combines multiple executive functions, are similar (Figure 6.11). The upper graph in Figure 6.11 illustrates the number of category changes mastered, while the lower graph compares the number of perseveration errors. As usual, early onset users do worse than late onset, who do worse than non-users. The higher perseveration scores reflect a decrease in mental flexibility – trying harder to make a failed strategy work. Alternatively, lower Wisconsin Card Sort scores reflect difficulty learning from mistakes.

Fontes concluded that exposure to marijuana during critical periods of brain development, i.e., early adolescence, may be more neurotoxic than later in adolescence. The dysregulation of fine-tuned developmental processes resulting from alternating excessive and deficient cannabinoid tone (i.e., clouds of marijuana's THC producing subsequent downregulated CB1 receptors) underlie the greater cognitive impairments in early onset marijuana use. While scientific reports often have to wait, sometimes years, to be replicated, Staci Gruber's Harvard team serendipitously confirmed Fontes' data later that same year. Gruber confirmed that early onset marijuana users (before age 16) perform worse than late onset users on a variety of frontal lobe-based executive function tests, including Stroop, Wisconsin Card Sort, and Trail Making.[23] In addition, she found that early onset users smoke twice as often and nearly three times as much marijuana per



Stroop Test (noun–colour) time in seconds in early-onset, late-onset, and control groups.
Error bars: 95% confidence intervals.

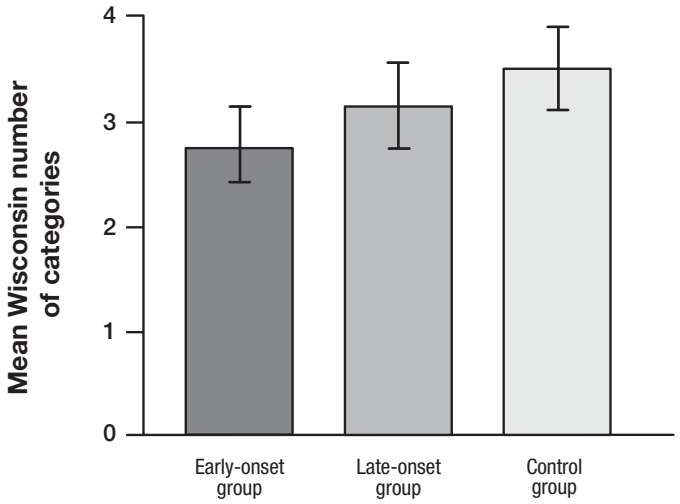
Figure 6.10 Marijuana impact on Stroop. Source: M. A. Fontes et al., "Cannabis use before age 15 and subsequent executive functioning," BJP 2011, 198: 442–7; DOI: 10.1192/bjp.bp.110.077479. Correspondence: Maria Alice Fontes, Rua Dr José Gustavo Busch, 155–121B Morumbi, São Paulo SP Brazil, ZIP 05705–190.

week relative to the late onset users. Gruber echoed Fontes when she concluded that early onset marijuana use disturbs fundamental brain maturation processes such as cell proliferation, migration, and differentiation regulated by the natural endocannabinoid system, including frontal brain regions responsible for higher order cognitive processes that are among the last functions expected to mature.[24]

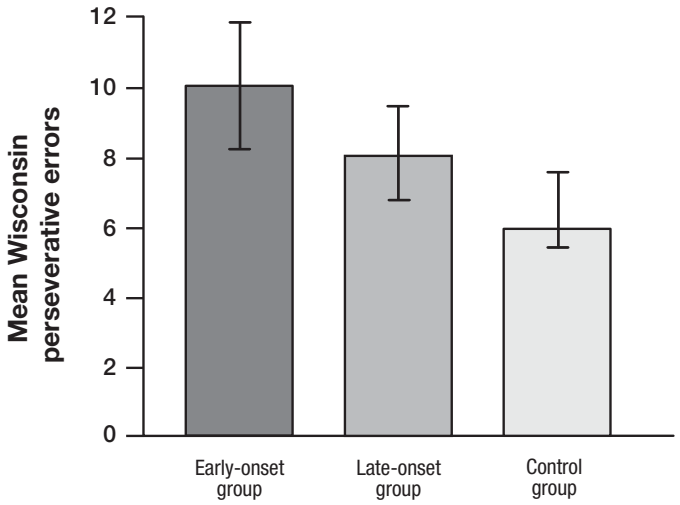
Fontes specifically rejects the alternative explanation that pre-existing impairments made some adolescents more prone to initiate marijuana use at an early age based on there being no difference in estimated IQs among early onset, later onset, and non-users. However, she does suggest the possibility that late onset individuals may use different neural networks to compensate for their deficits more than those who started at an earlier stage of brain development.

There are two separate lines of research that could be followed at this point. I will review the research referred to by Fontes on compensations made by the brain in reaction to ongoing marijuana use later in this chapter in favor of continuing exploration of the lasting deficits caused by excessive marijuana use during early adolescence.

The harbor and hills around Dunedin, New Zealand, are the remnants of a volcano, but an eruption of a different sort occurred in this city of 120,000 in 2012. The results of a 25-year study of 1037 Dunedin citizens born in 1972/1973 were published that year. Madeline Meier (now at Arizona State University) and a research team at Duke University analyzed data gathered by the Dunedin Multidisciplinary Health and Development Research Unit, which sought to determine whether the cognitive decline found in long-term marijuana users is concentrated among adolescent onset users. Marijuana use was recorded at ages 18, 21, 26,



Wisconsin Card Sorting Test number of categories in early-onset, late-onset, and control groups. Error bars: 95% confidence intervals.



Wisconsin Card Sorting Test perseverative errors in early-onset, late-onset, and control groups. Error bars: 95% confidence intervals.

Figure 6.11 Impact of marijuana use on Wisconsin Card Sort: Category changes and perseveration. Source: M. A. Fontes et al., "Cannabis use before age 15 and subsequent executive functioning," BJP 2011, 198: 442–7; DOI: 10.1192/bjp.bp.110.077479. Correspondence: Maria Alice Fontes, Rua Dr José Gustavo Busch, 155–121B Morumbi, São Paulo SP Brazil, ZIP 05705–190.

32, and 38. A battery of neuropsychological tests was conducted at age 13, before onset of marijuana use, and again at age 38.

Unfortunately, results of the Dunedin study have been widely misinterpreted. Careful reading is needed to understand exactly what the data proved. The original journal article is easy to misinterpret and even the U.S. NIDA does not clarify the results well on its website. As a result, the press and too many people believe that the more persistently adults use marijuana the more their IQ decreases. Somewhat buried in the article is this very important different conclusion [with emphasis added by author]: "In fact, *adult-onset* cannabis users did not appear to experience IQ decline as a function of persistent cannabis use."[25]

The findings of major importance in Meier's analysis are contained in the following list of facts confirmed by the Dunedin data:

- *The **only** individuals at age 38 who showed a reduction in IQ were those who were using marijuana at least once a week during adolescence.*
- Individuals who began marijuana use as adolescents are more likely to have persistent use as adults.
- The more persistently an adolescent onset user continues to use marijuana during adulthood, the greater is their reduction in IQ at 38.
- Those who began marijuana use the earliest and continued throughout adulthood lose an average of eight IQ points, which is sufficient to alter academic success and job opportunities.
- Stopping marijuana use did not fully restore neuropsychological functioning among adolescent onset former persistent cannabis users. Indeed, among adolescent onset former persistent cannabis users, impairment was still evident for one year or more after cessation of use.

Figure 6.12 illustrates the degree of IQ loss at age 38 for adolescent onset users depending on the degree of persistence of dependence throughout adulthood. *The graph also shows that individuals not dependent on marijuana before age 18 did not experience similar IQ declines even if they were dependent at multiple later assessments.*

Tests measuring IQ are comprised of an aggregate of several subtests. Analysis of the Dunedin data reveals that impairments in early onset persistent users are detected across five areas: Executive Functioning, Processing Speed, Memory, Perceptual Reasoning, and Verbal Comprehension, with the most robust findings being in executive functions and processing speed decrements. In addition, participants in the study were asked to identify an informant who "knew them well." These informants reported significantly more everyday life problems with attention and memory among individuals with the most persistent marijuana dependence. This confirms that cognitive deficits caused by marijuana are of more than academic interest, expanding Fisk and Montgomery's previous study in the UK of real-world memory lapses in marijuana users.[26]

The pattern emerging from scientific discoveries continues to become more obvious – from the location of CB1 receptor density to CB1 downregulation, damage to gray matter in the frontal cortex and hippocampus, loss of efficiency in axons within and between frontal lobes, the role of our endocannabinoid system in neurodevelopment and regulation of other neurotransmitter activity, to the timing of adolescent brain development and decrements in memory and executive functions found especially in early onset marijuana users. The continuum of links between different levels of investigation, from

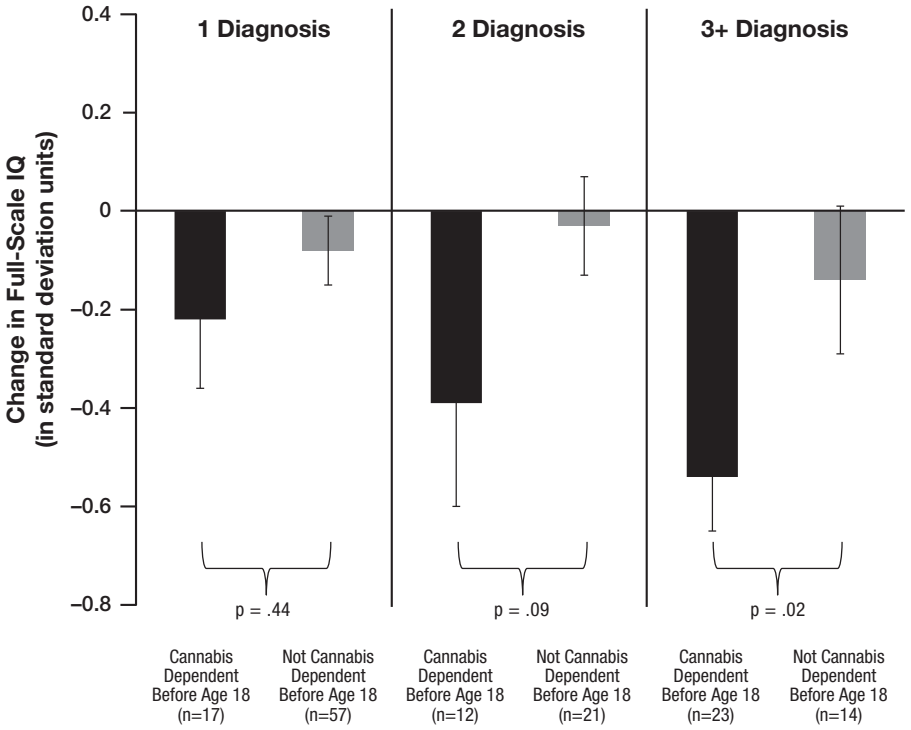


Figure 6.12 Decline in IQ at age 38 in adolescents dependent before age 18. Source: Meier et al., "Persistent cannabis users show neuropsychological decline from childhood to midlife," *Proc Natl Acad Sci USA*, 2012 Oct 2; 109 (40): E2657–64. Modification of Meier's Figure 2.

biochemistry to physiology and anatomy, from brain imaging to neurocognitive testing, behavior and reports from significant others becomes increasingly easy to recognize. Still, there is more. We need to review *all* the available data, until the pattern becomes undeniable.

Risk Assessment, Impulsivity, and Compensatory Processes

We can now explore the research introduced earlier in this chapter on compensations the brain makes in reaction to ongoing marijuana use. It is well known that the brain is highly plastic, meaning "capable of adapting to varying conditions." After strokes, remaining healthy brain tissue often adapts to serve functions previously served by damaged areas. Would similar adaptations compensate for structural deficits created by chronic marijuana use?

Back to University of California San Diego where Susan Tapert used a go/no-go experiment to explore the question of whether compensations occur in the brain in response to the impact of chronic marijuana use.[27] Tapert's go/no-go protocol presents a random series of large squares, small squares, large circles, and small circles one at a time for 200 milliseconds each. Individuals were instructed to press a button as quickly as possible every time they saw a shape (go stimuli) *except* for the small square (no-go

stimulus) – thus the name of this experimental protocol, go/no-go. Withholding the impulse to press the button when presented with the small square requires what is called response inhibition.

Tapert tested the same 16–18-year-old adolescents that Krista Medina used in her neurocognitive studies following 28 days of abstinence from marijuana. The average age of onset of use was 14 and participants in the study had used every other day on average for a total of 475 times. Marijuana users and non-users scored equally on their ability to withhold responses to the small square no-go stimulus, although both groups responded more accurately to the go stimulus than to the no-go, which is to be expected. Reaction times to the go stimulus were also similar between the marijuana users and non-using controls. In other words, there was no way to distinguish between the performance of abstinent users and non-users. On exit interviews, however, marijuana users indicated developing more perceptual strategies (e.g., "look for the small square to show up"), while non-users tended to use more cognitive strategies ("remember to hold off when I see that shape" or "concentrate").

Functional magnetic resonance (fMRI) imaging was performed during the go/no-go procedure. Tapert then subtracted the brain areas activated in both groups to obtain a map of additional areas active only in marijuana users (Figure 6.13).

This fMRI image visualizes for us the degree to which adolescent marijuana users activate larger areas of their brain during a response inhibition task (no-go) in order to perform as well as non-users, even after 28 days of abstinence. Tapert specifically noted that no areas activated in controls showed significantly less activation in users. On one hand, marijuana advocates may interpret these results to mean that marijuana helps people use more of their brain. On the other hand, an alternative interpretation is that marijuana decreases the efficiency of brain effort, leading to the need to employ more gray matter resources to compensate. In particular, since the frontal lobes provide inhibition, and regular use of marijuana diminishes frontal lobe function, additional brain areas need to be recruited to compensate for weakened frontal lobe inhibitory control. As we can see from Tapert's work, the compensation is sufficient to match the performance of non-users on the specific go/no-go task used.

A couple of years later an Australian collaborated with an Irishman to design a more complicated go/no-go protocol to investigate awareness, or unawareness, of errors.[28] Robert Hester and Liam Nestor's Error Awareness Task adds elements of the Stroop test by presenting the names of colors printed in congruent colors with an occasional incongruent color. Participants were to respond to each of the words by pressing a single 'Go trial' button and withholding this response under either of two different circumstances. Responses were to be inhibited if the same word was presented on two consecutive trials, and also if the word and font color did not match. These competing response inhibition rules were designed to increase the number of commission errors (i.e., committing a response that should have been inhibited). Sufficient practice was permitted before measuring performance to assure that the rules were understood (Figure 6.14).

In addition, participants were trained to press the button a second time if they committed a response to a no-go stimulus to indicate awareness of having just committed an error. The comparison of interest to Hester and Nestor was between aware and unaware errors, both in terms of performance and fMRI of brain activity. Marijuana users had, at a minimum, regularly consumed marijuana five to seven days/week for the

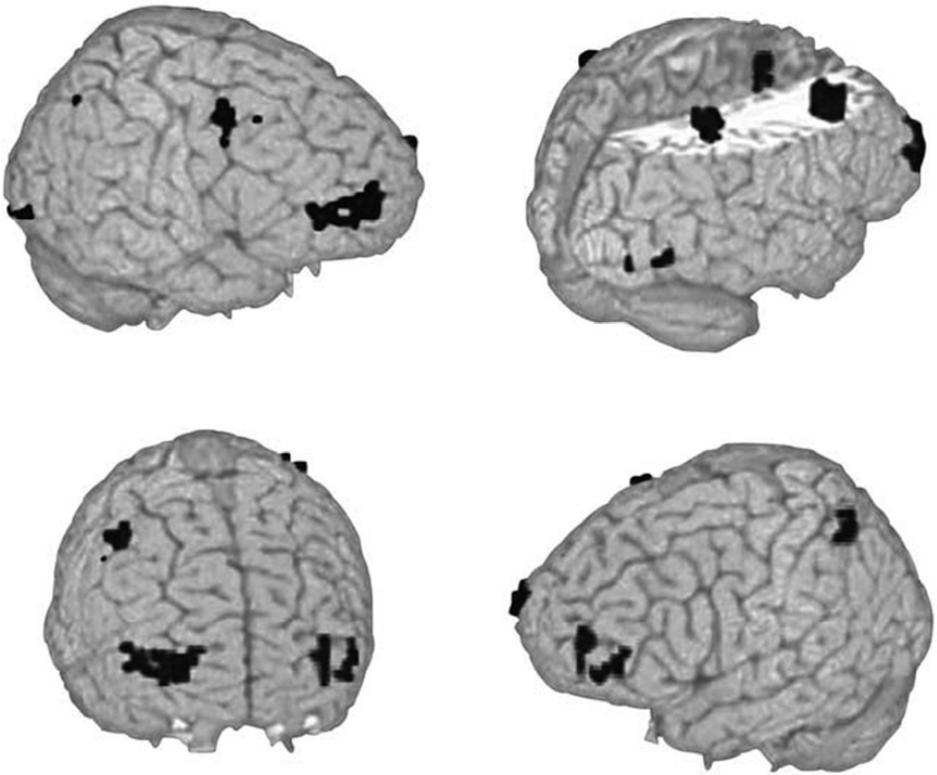
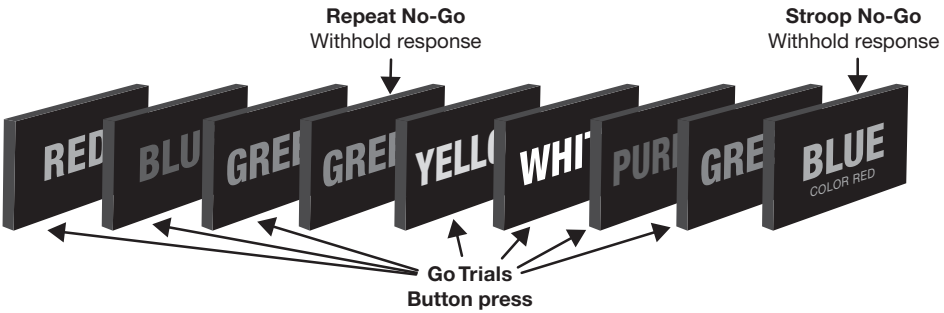


Figure 6.13 Compensation to chronic marijuana. Source: Based on Figure in Tapert et al., "Functional MRI of inhibitory processing in abstinent adolescent marijuana users," *Psychopharmacology (Berl)*. 2007 October; 194(2): 173–83. Converted to grayscale for purposes of this publication.



Font Colors Shown Above (Left to Right): **Red, Blue, Green, Green, Yellow, White, Purple, Green, Red.**

Figure 6.14 Go/No-Go task with error awareness. Source: Hester et al., "Impaired error awareness and anterior cingulate cortex hypoactivity in chronic cannabis users," *Neuropsychopharmacology*, 2009 October; 34(11): 2450–8. Note: Figure converted to grayscale for purposes of this publication.

previous two years and had smoked a minimum of 500 joints in their lifetime. The majority were young, high functioning adults in Dublin who had been using marijuana for the past eight years from an average onset age of 16.

It is absolutely necessary for science to demonstrate that its data is reproducible if it is going to establish objective facts. In this case, Hester and Nestor's use of a go/no-go protocol confirmed Tapert's finding of no difference in performance between marijuana users and non-users. Each group failed to inhibit responses as often as the other. However, they differed significantly in awareness of their errors. Non-users were aware of over 91% of their no-go errors, while marijuana users registered awareness of only 77% of their errors. While this discrepancy in awareness of errors was not relevant to performing the go/no-go task, it does represent a potential barrier to performance improvement. It is hard to learn from your mistakes if you lack awareness of them. Given the choice, I think most people would prefer more, rather than less, error awareness when attempting to improve performance on any task.

fMRIs also found complex differences between marijuana users and non-users. The most intriguing difference is that failure to recognize an error was associated in marijuana users more than non-users with less activity in an area of the brain called the anterior cingulate cortex (ACC, for simplicity), an area of cortex tucked into the midline of the two hemispheres. Current evidence suggests that the neural response to errors involves a network of regions that consistently includes the ACC.[29] Hyperactivity in the ACC is consistently seen in obsessive-compulsive disorder, a condition in which people consistently feel they have made an error (e.g., when turning off a light switch) requiring repeated double checking. Activity in the ACC prompts awareness of having made an error. Reduced activity is associated with a lack of error awareness.

The tendency toward inhibitory control or its opposite, impulsivity, significantly influences an individual's assessment of risk. The Iowa Gambling Task (IGT) is an experimental protocol that measures an individual's response to decision-making when risk and reward are involved. In 2005, Karen Bolla, at Johns Hopkins University in Baltimore, first reported the impact of marijuana on the IGT.[30] The IGT protocol presents four decks of cards to a person, who is told that each card they draw will win, or lose, variable amounts of game money. They are also told that some decks are more advantageous than others and that they would win more in the long run if they avoided the bad decks. The goal of the game is to win as much money as possible and participants were made aware of their running gain or loss. The task evaluates decision-making by measuring the participant's ability to choose between disadvantageous decks that yield high gains with a risk of extremely high losses (negative net score) and advantageous decks that yield low gains with a risk of even smaller losses (positive net score).

The average participant was 26 and had been using 41 joints a week for nearly eight years – regular heavy marijuana users – but were abstinent from marijuana for 25 days prior to being tested. Marijuana users performed significantly lower on the IGT than non-users, meaning that they chose more cards from the decks with higher gains and losses leading to lower net gains than the good decks with lower gains and losses but accumulating a higher net gain. When given a second trial, the marijuana users showed less learning (i.e., less improvement) than non-users. When the marijuana users were divided at the median between moderate and heavy users, the moderate group was found to perform as well as non-users. Only the heaviest users scored poorly. fMRIs performed during the IGT showed less activation in the frontal lobes in marijuana users

than non-users, with heavy users showing less activation than moderate users. Bolla drew the conclusion that "very heavy users of marijuana have persistent decision-making deficits accompanied by alterations in brain activity. Specifically, the heavy marijuana users may focus on only the immediate reinforcing aspects of a situation, while ignoring negative consequences." This result is a classic example of diminished executive function.

I am reminded of the basic science work of Giovanni Marsicano establishing the increased extinguishing of aversive memories caused by THC's stimulation of the endocannabinoid system (Chapter 2). I imagine that making mistakes is an aversive experience (really painful, embarrassing, or just a bummer) for most people. We generally feel bad, or even bad about ourselves, when we make errors. Fortunately, our endocannabinoid system helps our brain diminish the impact of painful memories, though hopefully not so quickly or completely that we cannot learn enough from the experience to avoid repeating it. Endocannabinoid-based forgetting of painful experiences is a great balm, just as our endorphin system offers a balm for pain, both physical and emotional. We can now see that the chronic use of marijuana sets in motion yet another process for being unaware. Both acute and chronic marijuana use minimize awareness of mistakes, which are important signposts for self-improvement if noted and responded to constructively.

A third mechanism for unawareness of mistakes, in the form of losses, caused by the chronic use of marijuana was described by Michael Wesley at Wake Forest University in North Carolina using finely detailed data from the IGT.[31] The daily marijuana users he compared to non-users averaged 26 years old and had been using for an average of nine years. The advance in his experimental technique was to separately analyze the beginning, middle, and final thirds of each person's performance, as well as to look at differences in brain activity between reactions to losses and wins during the first third of the task, which he called the strategy development phase. Everyone starts the task equally unsure of which decks are advantageous. A period of trial and error learning ensues as strategies are developed for how to maximize winnings. The following graph illustrates how much better non-using controls learn to perform, relative to the marijuana users, over the first, second, and third phases of the task (Figure 6.15).

Analyzing fMRI brain activity to losses during the first phase of strategy development explains why daily marijuana users failed to develop effective strategies as well as non-users. Non-users show increased brain activity in the ACC – the area where awareness of errors is generated – and the frontal lobe in response to losses, which predicted improved performance. Marijuana users show no such brain activity in response to loss.

Wesley used the IGT to reveal that the failure of daily marijuana users to develop successful decision-making results from a lack of response to losses that could aid strategy development needed for successful performance. The key deficit lies more in the undervaluing of loss than the overvaluing of gains. Daily marijuana use appears to blunt the response to negative stimuli. Called "chilling," we should not be too quick to forget that most of us look for ways to reduce the impact of negative experiences accumulated through the day. Whether the best way to achieve this serenity is by using marijuana is a value judgment each of us must make, hopefully with a clear mind, for ourselves.

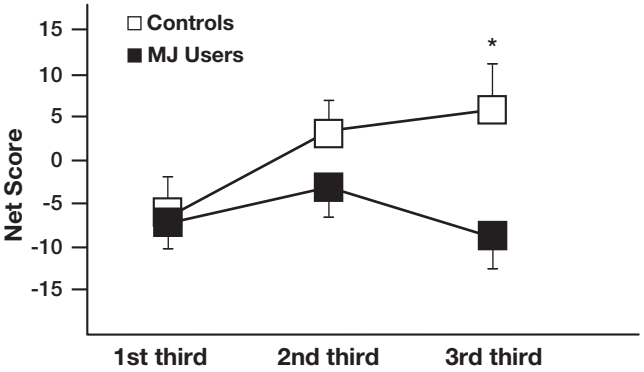


Figure 6.15 Marijuana impact on beginning, middle, and end of Iowa Gambling Task. Source: Wesley et al., "Poor decision-making by chronic marijuana users is associated with decreased functional responsiveness to negative consequences," *Psychiatry Research: Neuroimaging* 191 (2011) 51–9.

Wesley concluded that marijuana users do not process negative information in the same manner as non-users during ongoing decision-making, which, he noted, in a masterful understatement, "may result in inefficient strategies used to solve problems."

Awareness of errors and negative experience are not the only information that chronic marijuana users process differently. Chapter 7 explores evidence that awareness of subtle emotional cues is also reduced in persistent marijuana users.

Disentangling Cognitive Deficits from CD, ASPD, and ADHD from Marijuana Use

A recent prospective longitudinal study by Jean-François Morin finally provides data necessary to begin disentangling the cognitive deficits in CD, ASPD, and ADHD that create a vulnerability to marijuana use from the deficits produced by marijuana use itself.[32] The study assessed nearly 4000 students in the Greater Montreal region annually for four years, beginning in the 7th grade, on cannabis and alcohol use, recall memory, perceptual reasoning, inhibition, and working memory. Results confirmed the vulnerability hypothesis that decreased executive functions increase risk for early onset and heavier substance use. Individuals more likely to use cannabis showed lower working memory, perceptual reasoning, and inhibitory control prior to onset of use. This subpopulation of the cohort with cognitive deficits predating marijuana use would have included those with CD, ASPD, and ADHD.

Separately, however, as the frequency of cannabis use among the cohort increased over the four years, average performance for those with onset of marijuana use decreased on working memory, perceptual reasoning, and inhibition. These decrements were greater than for alcohol. More importantly, increasing cannabis use was associated with increasing impairments in delayed recall, perceptual reasoning, and inhibitory control for individuals (i.e., within-subject comparisons) without regard to the level of functioning prior to onset of use. Levels of cannabis use in this sample were low and infrequent but analyses nevertheless detected cognitive changes that were consequential secondary to small increases in cannabis use year over year.

A novel finding from this study is that changes in response inhibition following onset of cannabis use appear to be specific to cannabis and the study's authors noted the

consistency of their results with "animal studies showing that chronic administration of THC causes dose-dependent neurotoxic changes in brain regions that are rich in cannabinoid receptors, such as the hippocampus, amygdala, septum, and cortex, and [the fact] that abnormalities in hippocampal and temporal structures seem particularly linked to human cannabis use."

Another recent study focused on whether marijuana exacerbates symptoms of subclinical ADHD in late adolescents and young adults (aged 16–26).[33] Cannabis users and controls were evaluated for ADHD symptoms by parental report on a behavioral checklist. Both groups then completed a computerized continuous performance go/no-go test of reaction time, inhibition, and attention along with a battery of neurocognitive tests. Cannabis users demonstrated significantly slower response time on the go/no-go test. However, subclinical ADHD symptoms did not predict any attentional deficits. As a result, attention deficits seen in cannabis users were seen by the researchers as more related to cannabis use than to subclinical ADHD symptomatology.

In summary, animal studies on the cellular, structural, and behavioral effects of THC during adolescence combined with evidence that marijuana causes decrements in executive functions over and above any predating onset of use demonstrate that studies of the cognitive effects of marijuana are not significantly contaminated by inclusion of individuals with CD, ASPD, and ADHD.

Michael (Continued)

By the time I saw Michael his parents had already scoured the Internet for information about marijuana's impact on brain development and made what they found a frequent topic during dinner with Michael. The boy had no interest in talking science with me, but seemed intrigued by information about the level of use among his peers. Michael was incredulous when I told him the school survey showed only 6% of his classmates used as frequently as he did.

"No way," he insisted. "Ninety percent of the people I know are high most of the time."

That one comment let me know that Michael smoked on his way to school and didn't wait until 4:20 to get high.

"What do you like about being high?"

"Oh man, you never tried it?"

"This is not my first rodeo, Michael. I've talked to hundreds of people who use pot. People have very different experiences and like different things it does. You do know that, don't you?" I asked this question in a tone that took him into my confidence, assuming he would agree rather than feel challenged.

"Sure. I just like the body buzz and feeling good about myself."

"It's important to feel good about yourself. I get it. And my guess is that you don't just ***like*** *the buzz – you* ***love*** *it."*

"Yep. Better than a roller coaster."

"Do you remember when you first tried pot?" He nodded affirmatively right away and his eyes widened. "What was the best thing it changed?"

He thought a moment and then said, "How comfortable I felt. I fit right in."

"Sounds sweet. Did you feel uncomfortable much of the time before that, like you didn't fit in as much?"

"I guess," he tried to shrug off the significance of what he had just admitted to me.

"Let me see if I've got this straight. The things you value about marijuana is that it makes you feel more comfortable in your own skin, physically alive, and accepted by a group of friends. Those all sound like good things."

"You bet."

"And what do you know about how marijuana can do all these good things?"

He looked at me blankly, maybe shrinking back a little in his ignorance. That was all I needed to ask, "Would you like me to tell you some interesting things about how marijuana works?"

He shrugged, neither yes or no. I waited silently. Then he said, "Sure, I guess."

Maybe it was a sliver of an opening and soon I could begin exploring some of the negative ways marijuana might be affecting his mind.

When I next saw Michael's parents, they were more interested in talking about Michael's frontal lobes than about Michael the boy. I validated what they had learned about marijuana's impact on brain structure and said this helped them understand the urgency of acting to protect Michael's health and safety, meaning that Irene and Paul needed to think about how best to intervene in their son's use. At this point it looked unlikely that Michael had enough mental flexibility to change his perspective (shift set) on the role marijuana played in his life. I urged his parents to talk to Michael more about his social, emotional, and academic functioning than about his brain structure. Few adolescents are concerned about their frontal lobes, but far more dislike seeing their grades fall, friends change, and activities drop away. It is for this reason – the immediacy of current experience – that I focused their attention more on the functional impact of marijuana than on the impacts on brain structure. After all, adolescents smoking tobacco are usually far more worried about kissing with stale breath than about the remote prospect of lung cancer.

Meanwhile, I promised to work with Michael to see if he was aware of any problems marijuana might be causing, even as he was in thrall with it. Simultaneously, I would work with Irene and Paul to prepare a written contract of privileges, expectations, and consequences, including the possibility of drug testing and a wilderness experience during the summer if Michael was not willing, or able, to abstain from marijuana. (See Chapter 11 for more detail). For the time being Michael was more likely to pay attention to concrete consequences than abstract concepts.

Wilson

Wilson was a stereotypic 18-year-old stoner, complete with nascent blonde dreadlocks. Totally chill, nothing bothered him. He was not merely committed to using marijuana – he was devoted to it. With no plans for the future, he was seeing me for therapy only because his parents required it for his continuing to live at home after barely graduating from high school. He also came because he enjoyed arguing with me as a supposed authority from the straight world. He especially liked generating alternative interpretations to the scientific studies I described to him. Our relationship was one of worthy opponents, at best.

Wilson liked to call himself a "Chemical Zen Master – aware of everything and floating unperturbed through it all." I thought of him more as, in Pink Floyd's words, "comfortably numb," but he believed marijuana expanded his consciousness and made him hyperaware. In accordance with motivational interviewing principles, I began judiciously introducing scientific evidence to create cognitive dissonance in Wilson rather than attacking his beliefs directly. I carefully laid groundwork for discussing Hestor and Nestor's findings regarding error

awareness on their go/no-go protocol. When I described how marijuana users were not only less aware of when they had erroneously responded to stimuli to which they should have withheld a response, ***but also*** *that their fMRIs showed no brain activity in error detection locations (i.e., the ACC), he was temporarily thrown into doubt.*

"What if marijuana makes it harder to be aware of when I am unaware," he wondered aloud.

"Boggles the mind, doesn't it?" I asked, pleased he trusted me enough to acknowledge the data regarding regular marijuana users posed a problem. He soon shrugged off the annoying paradox, but I knew a valuable seed had been planted. I planned to present research about unawareness of emotional cues in regular users at a later time to reinforce his initial flicker of cognitive dissonance.

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Chapter

7

The Impacts of Ongoing Marijuana Use on the Mind: Section 2

Emotion, Motivation, Psychosis, and Practical Impacts

Emotion and Temperament

I now have the opportunity to present my favorite piece of research about the impact of persistent marijuana use. Staci Gruber, at Harvard, used a Masked Faces protocol to study the brain's response to emotional stimuli in heavy marijuana users (average age = 26, with age of onset at 15 and a minimum of 3000 lifetime joints).[1] She measured brain activity by fMRI while subliminally flashing a series of happy and fearful faces for 30 milliseconds, followed immediately by a neutral face for 170 milliseconds. The experience of participants in the masked face experiment is universally seeing only a series of flashing neutral faces. There is no conscious awareness of the preceding emotional faces, and participants are not required to take any action beyond watching the screen.

The amygdala (rich in CB1 receptors) has been well documented to be critically involved with processing emotion.[2,3] Despite no awareness of the subliminal fearful or happy face, the amygdala reacted to the fearful face – but only in non-users. No similar activity happened in the amygdala of chronic marijuana users to register the emotional stimulus. Figure 7.1 has remarkable power for a psychiatrist because it is literally a picture of unconscious brain activity in the non-user, and the lack of activity in the unconscious of the marijuana user.

Gruber concluded that chronic, heavy marijuana smokers do not process emotional stimuli in the same way as those who do not smoke; and this is true even when stimuli are below the level of conscious awareness. In another example of cautious scientific understatement, she notes that this may have negative consequences. In her words, "The ability to accurately perceive emotion and identify the affective states of others is critical for effective communication." Pity the poor spouses of regular marijuana users who chronically feel their partners are "not there emotionally."

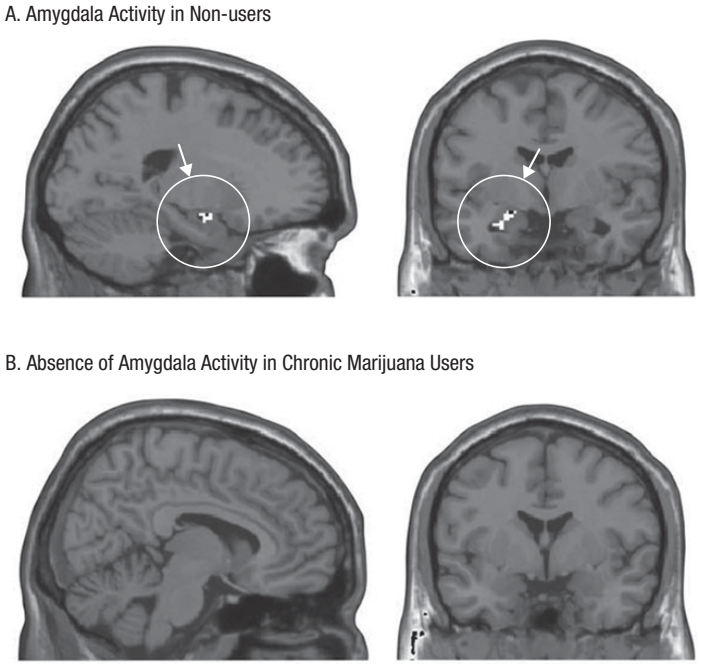

Figure 7.1 Masked faces protocol. Source: Gruber et al., "Altered affective response in marijuana smokers: An FMRI study," *Drug and Alcohol Dependence*, 105 (2009) 139–53.

The question of whether marijuana stimulates aggression and violence, always of interest to authorities regarding illegal drugs, was initially investigated in terms of acute doses. This question made little sense to many people who discovered the "love drug" in the 1960s; and, indeed, research generally found little relationship between marijuana and violence. Low doses were found to create a slight irritability and aggression when users were put under stress (as the Rolling Stones sang, "Hey, you, get off of my cloud"). But moderate to high doses clearly render people less likely to aggression and more likely to blend into their couch. (The question of drug cartel violence is irrelevant to whether the effect of ingested marijuana causes violence. Cartel violence comes from the impacts of money and power.)

The question of increased aggression during withdrawal from marijuana is more interesting. Budney showed that withdrawal from marijuana can produce irritability and anger roughly to the same degree seen in tobacco withdrawal. Specific measures of aggressive behaviors during total abstinence in heavy marijuana users finds an increase in incidence from day three through day seven, and totally subsiding within a month.[4] Complicating the matter is that withdrawal often exists in heavy marijuana users even without total abstinence. Similar to what is seen in heavy alcohol use disorders, withdrawal symptoms can be experienced merely as the result of falling blood levels of THC. In some cases of very heavy marijuana use, people alternate between being high and being in some degree of withdrawal irritability. The literature suggests that individuals with a history of aggression have an increase in rate of relationship aggression during

withdrawal, but there is no association between withdrawal symptoms and relationship aggression among those without a previous history of aggression.[5]

My own clinical experience in this regard is limited to observations that teenagers forced into abstinence by their parents can be quite verbally abusive, and occasionally physically threatening. However, whether this behavior is any more intense than when deprived of video games or their cell phone is still not entirely clear.

Perhaps the issue is more one of increased impulsivity, which could escalate irritability and anger into aggression. It is well known that individuals who are more likely to expose themselves to drugs of all types already have a tendency toward impulsivity. The regular and heavy use of marijuana is prone to increase this tendency in at least a couple of important ways. Van Laere's work on temperament and genetic differences in the density of CB1 receptors in the amygdala (Chapter 2) described how the amygdala's lessened response to novelty leads individuals to seek greater levels of novelty and thus have a more "extravagant," or unconstrained, personality. "Extravagance" is an aspect of novelty seeking defined as a form of "action impulsivity" reflecting a high appetite for the reward provided by novelty. Since marijuana provides experience both of "virtual" novelty and reward, people born with lower levels of CB1 receptors in the amygdala are set up to enjoy marijuana. At the same time, marijuana leaves further reduction of amygdala CB1 receptors in its wake by downregulating them. The impulse to act, and ultimately to seek and use marijuana would be further stimulated by this downregulation.

A second stimulus for impulsivity results from changes in white matter caused by chronic marijuana use.[6] In an earlier study, Stacy Gruber used fMRIs to measure altered frontal neural function in marijuana users performing the Stroop test of response inhibition.[7] In a follow-up study she first administered a self-report survey of impulsivity (the Barratt Impulsivity Scale) to non-users and chronic marijuana users (average age = 25, average age of onset = 15, average weekly use = 25 joints). As shown in previous studies, the marijuana users scored higher in impulsivity. She then used Diffusion Tensor Imaging to measure the health of white matter between and within the frontal lobes. The fiber tracts in question had deficits in their microstructural coherence that interfere with the normal one-way flow of water through axons. Gruber found a significant relationship between lower white matter fiber tract integrity in the frontal lobe and impulsivity scores in marijuana users. Weak linkages between frontal lobe neurons appear to diminish inhibitory control.

Given the above research on differences in how emotion is processed, the assessment of risk, the potential for aggression during withdrawal, and greater impulsivity, it is probably fair to conclude that chronic, heavy use of marijuana is capable of altering personality. Since adolescence is a time of psychological growth, it is very often difficult to tease apart those changes that are marijuana related from those that are part of an individual's development within the idiosyncrasies of their particular environment. The single most reliable method for discerning which changes are drug related is a substantial period of abstinence – a minimum of three months, and preferably six. While "clarity" is the word I most frequently hear to describe the impact of abstinence, I believe this refers to more than cognitive clarity. I sense "clarity" refers to dissipation of a cloud of unknowing that obscured emotional life as well.

Motivation

An "amotivational syndrome" has long been touted as a prominent symptom of excessive marijuana use. I personally had difficulty with this concept, primarily because I was unaware of any objective way to measure a person's motivation. From the outside, it is clear that many marijuana users lose interest in activities they participated in before the onset of marijuana use, and couchlock is a real enough phenomenon that many users readily acknowledge its existence. Even rats become "slackers" when given THC, preferring low effort/low reward tasks to high effort/high reward tasks that they are capable of performing.[8] Adding CBD in a 1:1 ratio with THC only partially attenuates the rats' unwillingness to make the effort to receive higher rewards.

Two interesting observations originally kept me from endorsing amotivational syndrome as anything more than an external description of lazy or disinterested behavior. Marijuana users seem highly motivated to obtain and continue using their marijuana. No lack of motivation there. Much of what parents call amotivational syndrome stems from their dislike for a child's motivation waning for things the parents value – sports, a part-time job, and academic achievement. It is painful when a child does not take advantage of opportunities that lead to career paths parents approve of, whether marijuana is involved or not.

Second, I have seen what others call amotivational syndrome more as a novelty deficit condition. Those adolescents who tend to be rewarded most by novel experiences will be drawn by the pharmacologic enhancement of virtual novelty. Some marijuana users are drawn into an internal world, while others find fascination in repeated experiences of fast action external realities – video games, skateboarding, etc. When not high, however, much of the world lacks enough sense of novelty that no one would be motivated to engage in its blandness.

However, a research team at the University of Michigan led by Meghan Martz recently provided a new perspective on amotivational syndrome when they discovered a reward deficit for non-marijuana related experiences in regular marijuana users. Motivation depends on anticipation of reward, and so Martz chose to investigate the effect over time of marijuana use on a monetary incentive delay task. Each trial of this experimental protocol begins with telling participants the test could win or lose them a small ($0.20) or large ($5.00) monetary reward, or nothing. They were instructed to focus on a fixation point and to press a button when a target stimulus appeared. Functional magnetic imaging recorded brain activity during this monetary incentive delay task.

Martz ran the study on each individual at ages 20, 22, and 24. Marijuana and other drug use were evaluated annually. She focused on fMRI activity in the reward center (nucleus accumbens) and found no difference in activity between marijuana users and non-users during anticipation of financial reward at age 20. However, during the subsequent two trials, at ages 22 and 24, those who had the greatest level of marijuana use during the previous year had corresponding reductions in the reward center's activity in anticipation of financial reward. The study's findings indicate that continued marijuana use might blunt the brain's response to nondrug rewards.[9] She concluded that the effects of long-term marijuana results in a general blunting of reward response. The salience (i.e., the quality of being particularly noticeable, important, and desirable) conferred by the nucleus accumbens onto a monetary reward had diminished over time for regular

marijuana users. This would have an obvious impact on motivation, *ergo* an amotivational syndrome based on reward deficit. (Of course, marijuana users can always counter that pot has enlightened them to become less materialistic. The challenge to this argument is always animal data showing similar motivational changes caused by THC.)

An interesting wrinkle exists in the people studied by Martz that requires some interpretation. Participants were drawn from the Michigan Longitudinal Study, which is based on familial risk for substance abuse disorder and 78% were known to be at high risk for SUD. By the third trial, at age 24, 31% met diagnostic criteria for addiction to marijuana. While choosing to test this high-risk population all but guaranteed that Martz's study would contain individuals who significantly increased their marijuana consumption between ages 20 and 24, the choice also introduced the complication of predisposing factors causing the reward blunting rather than marijuana. On the other hand, she may have demonstrated that these underlying factors not only increase the likelihood of marijuana use, but also increase the brain's susceptibility to blunted brain activity in anticipation of non-marijuana rewards. Blunted anticipation of reward would certainly unmotivate most of us. The topic of amotivational syndrome continues to provide rich opportunities for more creative research.

Marijuana-Induced Acute Psychosis and Schizophrenia

The question of whether marijuana (or hashish) use can cause psychosis is over a century old. During the British occupation of Egypt, the prominent Scottish psychiatrist, Thomas Clouston, visited the Cairo asylum in 1896 and noted that 40 out of the 253 patients had insanity attributed to hashish.[10] With the global increase in marijuana use since then, and now with increasing legalization, considerable effort has been put into understanding the potential relationship between marijuana, acute psychosis, and schizophrenia. No issue is as emotionally charged for concerned parents as the possibility of marijuana's causing schizophrenia in their child. And few moments are more painful for health professionals than having to inform parents that their child is exhibiting symptoms of schizophrenia and not merely the temporary effects of too much weed.

It is important to make a clear distinction between two separate phenomena potentially related to marijuana use. The concept of an acute psychotic condition induced by marijuana is not the same thing as the possibility of marijuana's causing, uncovering, or worsening the chronic, severe mental illness called schizophrenia. The more general term "psychosis" labels a variety of conditions characterized by impaired reality testing, e.g., delusions (false beliefs), hallucinations (responding to internal stimuli as objective reality), formal thought disorders (loss of logic such as reversal of cause and effect), and at least a temporary loss of awareness of one's misperception of consensual reality. The presence of psychosis requires diagnostic investigation. Psychotic conditions develop from a wide variety of causes, from ingesting toxins to liver failure, Parkinson's disease, head trauma, extreme sleep deprivation, and serious mental illness. In the most general sense, psychosis exists when a person does not realize he or she has lost touch with external consensual reality. Therefore, someone very high on marijuana can have psychotic *symptoms* such as experiencing himself or herself diffusing into the vast universe without being psychotic if he or she understands they are still sitting on their living room couch.

Schizophrenia, on the other hand, is a serious brain-based mental illness that causes profound, and often intractable, psychosis. The formal diagnosis of schizophrenia entails a host of positive symptoms (feelings, thoughts, or behaviors that are not normally present) and negative symptoms (or deficits), a typical age range of onset, and prognosis. Positive symptoms include delusions, fragmented thoughts and speech, disorders of logic, and hallucinations. Negative symptoms include deficits in emotional and interpersonal responses, flat or inappropriate affect, poverty of speech, and lack of pleasure (anhedonia) or motivation. Symptoms usually begin gradually during late adolescence or young adulthood and last a lifetime. A hereditary component often contributes to schizophrenia.

Many difficulties complicate researching the relationship between marijuana, psychosis, and schizophrenia. There is no adequate animal model for psychosis or schizophrenia. Unlike research on the relationship between tobacco and cancer, there is no research protocol similar to rubbing tobacco tar on rat skin to see if cancer develops. Furthermore, there is no ethical way to design controlled experiments in which humans are randomly assigned to either marijuana-use or non-use groups to see if psychosis occurs more frequently in either group. This has left two avenues for research; one being to study the possibility that marijuana can cause acute psychosis among those who choose to use it and the other being epidemiological and genetic studies of the relationship between marijuana use and the diagnosis of schizophrenia. Such studies also suffer from the complications that marijuana users consume different strengths and varieties of marijuana and often other drugs and alcohol as well.

While reports of marijuana producing psychotic symptoms acutely have been in the literature for over a century and a half, it is only within the past few decades that research has gathered any substantial data.[11,12] The question of whether marijuana alone can cause psychosis has more recently been investigated by actually administering intravenous THC to healthy adult volunteers. Transient psychotic symptoms (measured by the Positive and Negative Syndrome Scale – PANSS) result in 50% of people after 30 minutes, when the blood level of THC is highest.[13] The IV dose of THC used (2–5 mg) approximates the blood level after smoking one joint of 1–3.5% THC marijuana (considerably lower than marijuana used today). Of particular interest is the fact that administering cannabidiol (CBD), which is present in varying amounts in marijuana, prior to THC reduces the resultant paranoia and psychotic symptoms.[14] Although IV THC causes anxiety in most people, there does not appear to be any relationship between the degree of anxiety and the appearance of psychotic symptoms. Furthermore, frequent marijuana users have fewer psychotic symptoms in response to IV THC, though it is not yet clear if this is due to the development of tolerance, an inherent physical or psychological quality characteristically found in regular users, or the effect of learning what to expect and how to "maintain" (i.e., use compensatory strategies to appear normal).[15] The most common reasons for acute visits to emergency rooms following an overdose of marijuana is a panic reaction, not psychosis, and this occurs more frequently in naïve users and those unfamiliar with the slower onset of edibles, which too often leads to impatiently taking additional doses that accumulate to toxic levels. Although published studies of these topics are sparse, a quick review of Internet postings is convincing. For example:

> anecdotal reports suggest that "... it is the novices who seek out hospital services when they're ... thinking they're dying, when they're actually having a panic attack. The

> proliferation of edible marijuana products (cakes, cookies, sodas, etc.) – which was typically a novelty item for stoners in the past, but is now a well-marketed and tasty pillar of the industry – can also be an attractive alternative to smoking for novice users, who often commit the common mistake of eating the recommended dose, not feeling anything 20 minutes later, and then eating *way* too much."[16]

This phenomenon is seen, for example, in tourists leaving the Denver airport who suddenly realize it is illegal to carry their souvenir edible cannabis to their home state, make a rash decision to consume it while waiting for their flight and then become "too high to fly" and end up in a hospital emergency room with a panic attack.

The relationship between marijuana use and schizophrenia is a more complex question. First coined by Eugen Bleuler in 1908, schizophrenia is a long-term psychotic illness involving disordered thought, emotion, and behavior, leading to faulty perceptions and feelings that result in withdrawal from reality and personal relationships into preoccupations with fantasy, delusion, and internal stimuli (i.e., hallucinations). A sense of derealization and mental fragmentation occur. Onset tends to be in late adolescence or early adulthood and is seen more often in males. The accepted rate of schizophrenia in the general population is ~1%.[17]

Determining the relationship between schizophrenia and marijuana use with *scientific* certainty encounters a true "chicken and egg" dilemma, despite the convictions of parents who have painfully watched a child descend into schizophrenia while using marijuana. Epidemiologists repeatedly find higher rates of schizophrenia in marijuana users than non-users, and higher rates of marijuana use in schizophrenics than in healthy populations, but cause and effect have been extremely difficult to absolutely prove. The first large study of this relationship, published in 1987, asked 45,750 Swedish army conscripts about their drug use. Those who had used marijuana more than 50 times were six times more likely to develop schizophrenia over the next 15 years than those who had never used it.[18] Meta-analysis, which combines results from multiple studies, increases the power to estimate the size of any effect. Meta-analyses show a two-fold increase in psychotic outcomes for average marijuana users and an almost four-fold increase for the heaviest users compared to non-users, though this remains only an association between marijuana and schizophrenia and not proof of causation.[19]

There are more factors complicating research of the association between marijuana and schizophrenia than you can shake a stick at. One very important factor appears to be what variety of marijuana, and how much, is being used. Those who use very high potency marijuana (e.g., "skunk") on a daily basis have been found to be five times more likely than non-users to suffer from a psychotic disorder.[20] On the other hand, a Dutch survey found that those who prefer marijuana with the highest CBD content do not experience as great an increase in psychotic-like experiences.[21] Similarly, hair analysis shows that users with both detectable THC and CBD have fewer self-reported psychotic symptoms than those with only THC.[22] These findings regarding CBD are consistent with the beneficial effect on psychotic symptoms of administering CBD before intravenous THC. However, this effect should not be taken as proof that CBD is an effective antipsychotic, since its action here is at least partially due to its reduction of THC's negative impact. Strains of marijuana that are especially high in THC are necessarily low in CBD, since both are derived from the plant's precursor CBG, and so no marijuana can be high in both.

Putting aside the question of *causality* for the moment, we can look at research on the nature of the *association* between marijuana and schizophrenia (i.e., 2% for moderate use and 4% for heavy and early onset use). Marijuana users who do develop schizophrenia tend to have a significantly earlier onset of psychosis than those who never used,[23] on average six years earlier for users of high potency marijuana,[24] and a more severe course of illness.[25] Schizophrenics who continue marijuana use have higher relapse/rehospitalization rates, longer hospital admissions, and more severe symptoms than either former users who discontinued marijuana or those who never used.[26] In an extraordinary experiment, THC was given to schizophrenics, who then experienced transient exacerbations of their psychotic symptoms, which speaks to the importance of schizophrenics avoiding marijuana use.[27] Furthermore, schizophrenics who use marijuana show a more pronounced reduction in brain volume over a five-year period than schizophrenics who do not use marijuana.[28] The current evidence overwhelmingly justifies the conclusion that marijuana is harmful in schizophrenia for a variety of reasons, some of which could potentially be causal.

Most recently, a novel research design by Marta Di Forti surveyed 11 sites across Europe and correlated variations between the sites in patients aged 18–64 experiencing first-episode psychosis with data on the expected concentration of THC in the different types of cannabis available at each local site.[29] Daily use of greater than 10% THC increased the odds of a psychotic episode nearly five times the rate of psychotic episode found in those who never used cannabis. Di Forti concluded that differences in frequency of daily cannabis use and in use of high potency cannabis contributed to the striking variation in the incidence of psychotic disorder across the 11 studied sites. While there is always a temptation to jump to the conclusion that new data proves a causal connection between cannabis and schizophrenia, a commentary accompanying Di Forti's article cautions that data from intriguing genetic research raises the possibility that the relationship is bidirectional.[30]

Genetic research has begun to further clarify the relationship between marijuana and schizophrenia. No single gene causes schizophrenia, but researchers are identifying a host of genes that all appear to contribute to the illness. The more of these genes an individual has, the greater risk they have for developing schizophrenia. As a result, we can now analyze an individual's polygenic risk score. It turns out that the higher schizophrenia polygenetic risk score an individual has, the greater likelihood they have of using marijuana, and using greater amounts.[31] This raises the possibility that, for some people, the association between marijuana and schizophrenia is due to a shared genetic source. One study found that those adolescent males with high schizophrenia risk scores who used marijuana have decreased cortical thickness compared to boys with the same risk score who did not use marijuana; and the more marijuana they used, the greater the decreased thickness.[32] These results suggest that some individuals are more vulnerable to marijuana's association with schizophrenia than others. It remains unclear whether this is entirely due to marijuana directly raising the risk of schizophrenia in vulnerable individuals, or whether the same genes that increase the risk for schizophrenia also increase the risk of marijuana use.

The profound genetic and statistical complexity involved with attempting to establish the degree to which marijuana may, or may not, *cause* schizophrenia is reminiscent of the difficulty scientists had "proving" that tobacco causes lung cancer. With so many variables in play, including a marijuana industry with its devoted community resisting bad

news, massive numbers of people need to be studied to achieve a high enough level of probability to be conclusive. This is now being pursued through human genome research. The first mapping of an individual's entire DNA sequence was completed in 2001 after 13 years and $1 billion. Technological advances have automated what was a laborious manual task to the point that an individual's entire genome can now be sequenced in less than 24 hours for under $500. Researchers who compared single molecule DNA variants in over 34,000 marijuana users to over 45,000 non-users claim to have found strong support for a causal link between the use of marijuana and an increased risk of schizophrenia.[33] Human genome studies have discovered single molecule variants associated with people who have used marijuana. Individuals with these variants have been found to have an increased incidence of schizophrenia independent of whether they ever used marijuana or not. In other words, use of cannabis is causally related to risk of schizophrenia, i.e., the two share the same genetic risk factor.[34] It is simply too early, and the research techniques used are too new, to know whether these claims of causality will hold up under the scrutiny of other scientists. Only time will tell. Even if this research is verified, it still does not mean that the use of marijuana causes the onset of schizophrenia, but merely that the two share a common cause.

We need to draw back from getting totally lost in the research weeds regarding the relationship between marijuana use and schizophrenia. In my clinical work, I do not need to ask parents of a psychotic, marijuana-smoking adolescent whether they think pot has driven their kid off the rails. They *know* marijuana is making their son (most often) or daughter crazy. Their child feels lost to them, no longer who they knew since birth, suddenly a stranger inside a familiar body. To paraphrase the famous rock group Pink Floyd, there's someone in his head, but it's not him.[35]

I listen to parents' pain, but remain aware that our direct experience is not scientific evidence, no matter how personally convincing it seems. We all lead statistically insignificant lives and no number of individual anecdotes ever amounts to data. So, I need to offer parents the best scientific explanation currently available for what is happening to their child. I have come to believe, although this may eventually prove to be simplistic, that there is some overlap between the group of genes that contribute to marijuana addiction and those that contribute to schizophrenia. What these genes do may be nothing more than to increase our vulnerability, to diminish our resilience, and to weaken links in the chains that anchor our health. The more of these genes we inherit, the greater is our risk of adverse outcomes.

We may all carry some risk for schizophrenia. For the vast majority of us, this risk is so minimal as to be nearly nonexistent. But for 1% of us, the risk is large enough to make schizophrenia inevitable. For these unfortunate individuals, the evidence says that marijuana use makes the illness even worse. And then there are those individuals whose risk for schizophrenia is subclinical – not high enough to make schizophrenia inevitable, but high enough that their brain can be pushed over the edge into psychosis by marijuana (among a wide variety of other stressors). Those people on the edge of schizophrenia who also are genetically vulnerable to marijuana addiction are doubly star-crossed. Early and heavy marijuana use, especially high THC marijuana, tips the scales to activate schizophrenia, and the resulting delusions often fan the flames of further marijuana use and addiction. In a very real way, the association between marijuana and schizophrenia might be bidirectional in causation, resulting in a runaway freight train, just as wind and a small spark can combine to create an uncontrolled forest fire.[36]

Fortunately we have solid evidence that discontinuing marijuana use generally reduces relapse rates and symptom severity in schizophrenia.[37] This raises abstinence from marijuana to the highest priority for anyone experiencing psychotic symptoms. Unfortunately I have too often heard a clinician ignore marijuana use by a schizophrenic patient in an effort to "not take away one of their few pleasures."

Finally, although we must always resist the temptation to overvalue the most recent research article to appear, new data from Canada appears to support the idea that all young marijuana users are put at risk of psychotic symptoms characteristic of schizophrenia. A mid-2018 Research Letter published online by *JAMA Psychiatry* reported a study demonstrating a clear association of cannabis use frequency with increased psychotic symptoms, and not vice versa, in the general population at a developmental stage when both phenomena have their onset.[38] The prospective study of 3720 adolescents in the Greater Montreal area used a web-based annual survey to obtain self-reports of past-year cannabis use and psychotic symptoms over four years, from age 13 to 16. Anonymous self-reports of drug use have been proven to be the most effective measure of what is often sporadic and low-level drug use during early adolescence.[39] Marijuana use in any given year was found to predict an increase in psychotic symptoms a year later, and not the other way around, a result that may have begun to tease apart the chicken and egg problem of causality. And because the existence of psychotic symptoms is a predictor of increased risk of developing schizophrenia, the lead researcher, Patricia Conrod, concluded that "It's extremely important that governments dramatically step up their efforts around access to evidence-based cannabis prevention programs."[40]

Practical Impacts of Chronic Marijuana Use

Differences in brain imaging or laboratory cognitive testing between marijuana users and non-users is meaningless to most people unless there are also palpable practical differences between the lives of users and non-users. But science leaves us in a mostly gray area here. The chicken and egg conundrum dominates efforts to delineate differences between the course of people's lives with or without regular marijuana use. Statistics reveal different levels of achievement between the two groups, but many individuals defy the statistics and achieve both objective and subjective success despite regular marijuana use. And just as many people who never use can fall well below the norm for non-users. Considerable sophistication is required to weed through the overwhelming number of variables influencing people's lives to understand the few facts that have been established about the long-term impact of persistent marijuana use. These facts will only tell us what outcomes are generally *associated* with regular marijuana use and not what outcomes are necessarily *caused* by marijuana.

Because marijuana policy in Australia and New Zealand has been remarkably free of politics and ideology compared to the U.S., public health and science have guided both their policies and research. While Madeline Meier reported a decline in IQ among early onset marijuana users at age 35 in the Dunedin study, other researchers have reported on the details of their progress as young adults. David Fergusson investigated the educational achievement associated with adolescent and young adult marijuana use and found that young people who had used marijuana more than 100 times dropped out of school 5.8 times more often than those who had never used marijuana.[41] While 100 uses may sound large to many people, it is not that hard to achieve – once a weekend for two years,

or Friday and Saturday for one year. Those who had never used marijuana were 3.3 times more likely to enter university and 4.5 times more likely to graduate than those who had used marijuana on at least 100 occasions.

A fascinating natural experiment in the Dutch city of Maastricht is worth reviewing here.[42] Maastricht is close to several other countries, including Germany, Belgium, France, and Luxemburg, which led to becoming a major hub of pot tourism at its local cannabis shops. When officials decided to restrict this tourism in 2011, all nationalities other than Dutch, German, and Belgian were no longer able to purchase marijuana legally. Researchers followed the impact of this policy on students at Maastricht University. Students not from the Netherlands, Belgium, or Germany suddenly had a significant increase in grades by 11% of a standard deviation and an increase in pass rates by 5.4% when banned from entering cannabis shops. Grade increases were most notable in courses requiring numerical/mathematical skills. Significantly, there was no difference in study time between students who had legal access to marijuana and those who did not. When the restriction on access was lifted after four months, the academic benefits experienced by foreign students were lost. These results appear to have considerable pragmatic meaning.

While the data suggesting early heavy use of marijuana is associated with educational dropout, Fergusson raises the possibility of a reverse causal association in which the experience of early school dropout encourages increased use of marijuana. The chicken and the egg are inseparable. Marijuana causes school failure, which encourages marijuana use, which causes greater failure, and so on. Initially, confounding family and social variables led Ferguson to conclude that the association between marijuana use and lack of school achievement "reflects the effects of the social context within which marijuana is used rather than any direct effect of marijuana on cognitive ability or motivation." After following the same Dunedin population for an additional five years Fergusson reported on a wider range of negative outcomes encountered by regular marijuana users.[43] He found that the lack of educational achievement was generalized throughout other areas of life. The higher the marijuana use between 14 and 21 years, the worse were a range of associated outcomes by age 25. The income of those who had used 400 times or more was 76% of those who had never used. Welfare dependence was 3.6 times higher. Unemployment was 2.6 times higher. And self-reported levels of relationship and overall life satisfaction were lower. While cause and effect are still unclear, and many might welcome the balm marijuana offers for a less than satisfying life, Fergusson now concluded that his data were consistent with a "growing body of knowledge regarding the adverse consequences of heavy cannabis use."

The "growing body of knowledge" received confirmation in a study of Boston area residents.[44] Apparently Kiwis are not the only population for whom objective and self-report measures show a range of negative features associated with long-term heavy marijuana use. Looking at individuals, age 30–55, half of whom had smoked marijuana 18,000 times or more and all of whom had smoked marijuana a minimum of 5000 times in their lives, a large majority report a "negative effect" of marijuana on their cognition (90%), memory (90%), career (79%), social life (70%), physical health (81%), and mental health (60%). These results echo an earlier Australian survey, with an intriguing wrinkle.[45] Almost all of the 268 long-term heavy users in rural Australia reported some negative aspects of marijuana use, with 21% reporting anxiety, paranoia, or depression,

and 21% reporting tiredness, lack of motivation, and low energy. On the other hand, 72% said the benefits outweighed the risks; 21% reported an even balance between positive and negative effects and only 7% felt marijuana had done them more harm than good. I am not sure if this striking difference from Boston natives reflects the Australian character, a stark outback environment known for marijuana cultivation, or differences in the survey questions.

A notable finding in the Boston survey is that the levels of education and income in families of origin were similar for heavy users and non-users, but the users had significantly lower levels of educational achievement and income than non-using controls. Nearly 50% more non-users earned over $30,000 than heavy marijuana users. Satisfaction with the quality of life is also reduced in heavy marijuana users compared to non-users, including satisfaction with self and life (34% versus 53%), happiness (47% versus 60%), and intimate relationships (33% versus 45%).[46]

The most recent, and most comprehensive, effort to understand the long-term consequences of adolescent cannabis use combined a variety of data sets from both New Zealand and Australia.[47] The study found a clear and consistent dose-response relationship between the frequency of adolescent use and all adverse young adult outcomes at age 30. The odds of completing high school were 63% lower for daily users before age 17, and 62% lower for graduating from college than those who had never used marijuana. Other illicit drugs were used eight times more often and the odds of suicide attempt were seven times higher. Rates of depression and welfare dependence were both higher in marijuana users. The study's authors concluded that "efforts to reform cannabis legislation should be carefully assessed to ensure they reduce adolescent cannabis use and prevent potentially adverse developmental effects."[48]

There are no chickens without eggs, and no eggs without chickens. We need to see chickens and eggs as two facets of the same phenomenon. In a similar way, we need to see the heavy marijuana use associated with lower achievement and less satisfaction with adult life as two facets of the same phenomenon. The two facets mutually reinforce each other. Youth at risk for a variety of reasons, whether family discord, physical or sexual abuse, violent environments, poverty, etc., may be more likely to use marijuana, and marijuana use increases their risk for adverse outcomes.

Robert

"At 39 years old, Robert had a solid career as representative of a major clothing brand with Northern California as his lucrative territory. His wife was a high school teacher and the oldest of his two daughters was just approaching her teenage years. His marriage was stable, except when his wife discovered once again that he had not given up his secretive marijuana use. Her major complaints about his use were what she called Robert's emotional distance, his hiding it from her and fear that their daughters would soon realize their father still smoked pot. They came to see me when she found him getting high in the attic while the girls were home. Robert appeared both contrite and defiant.

"I am picking up two feelings from you at the same time, Robert, and I am interested in both of them. You seem both apologetic and angry. Am I right?"

"My wife can be a real Nazi about marijuana."

"I am not a Nazi about marijuana," she interrupted stridently. "You know I enjoyed it as much as you before the girls were born . . ."

I held up my hand to stop her, recognizing that Robert needed more support to open up than she did.

"You see how witchy she can be," he said. "I just don't see anything wrong with it, and it works better than any antidepressant I've ever taken. Mostly I use it on business trips, not at home." He paused. "But I really don't like lying to you," he said in a conciliatory tone to his wife.

"I can see you are serious about not liking being dishonest, but I can see your wife doesn't feel she's being taken seriously."

"I don't think you take my worry about the girls seriously. You just don't seem fully present with me. I see kids at school going down the drain all the time because of marijuana. And our daughters are getting to the age when it's going to be available, and attractive. Having a father who can't stop is a bad role model."

"I can stop if I want to," he objected.

"I am glad that is established," I said.

"I stop all the time," he added wryly, trying to lighten the mood.

"Right," I smiled. "What interests me is your wife's complaint that you are not emotionally present." I turned to her. "Can you tell me more what you mean?"

She teared up immediately and had trouble talking. "It's just, I don't know, Robert isn't fully there when he's stoned, and sometimes for a few days after, though I never know for sure when he's using and when he's not."

"Not there? Can you put a little more meat on the bones so I understand better?"

"I mean that he doesn't react back when I'm obviously feeling something."

I felt her distress and looked at Robert, but he said nothing, seeming to prove her point.

"If it's OK, I'd like to show you something. But I don't want you to say anything before Robert has a chance to react first. If that's OK, do I have your promise?"

She agreed and I showed them the figure from Staci Gruber's research on how regular marijuana use reduces the amygdala's response to emotionally charged faces. After letting some time lapse, I turned to Robert.

"Seeing is believing," he said with resignation.

Jim

Jake was 45 years old, a divorced contractor with one child, a 20-year-old son named Jim. Two years ago, his ex-wife had called to say she no longer felt safe with Jim living with her. He had recently begun talking about the Ku Klux Klan and the National Rifle Association following him and sending him threatening texts that disappeared as soon as he read them. Then his behavior started becoming more bizarre, including ripping the pocket in his shirts before putting them on and washing the bottoms of his shoes several times a day. When he began walking around the house with no clothes on, his mother asked Jake for help taking their son to the emergency room.

Jake had long taken a hard-nosed attitude toward Jim's marijuana use and now insisted on bringing the boy under his wing to straighten him out. Jake read his son the riot act, inspected things Jim brought with him from his mother's to be sure there was no pot and started observed urine drug screens twice weekly. He also insisted on an addiction medicine evaluation and treatment for what Jake saw as marijuana addiction. Under Jake's protection, much of the strange behavior ebbed away, but Jim still seemed flat, unmotivated, and isolative.

When Jim walked into my office he almost looked like a perfectly normal young man. There was a slight hesitation as he sat in the chair I offered and his eyes darted around the room as if checking me out. I noticed a small rip in his shirt pocket.

"Welcome. What brings you to see me?"

"My dad."

"Why does he want you to see me?"

"Marijuana."

"What about marijuana."

"Too much." Not only were his answers sparse, but his tone was distant, not fully involved in our conversation.

"Your dad smokes too much marijuana?"

He looked up at me for the first time with a bellow of laughter followed by quiet giggles to himself as he shook his head "No."

"Why is that so funny?"

"That would be like having an FBI narc for a father who was a secret stoner. But maybe, I suppose. Strange things happen all the time."

"I guess. Are any strange things happening to you?"

He looked around and lifted a hand to his shirt pocket but said nothing.

"Is there something in your pocket?"

His hand immediately darted into his pocket and searched around. He was suddenly agitated and blurted out, "Nobody put anything there."

"Who would put something in your pocket without your knowing it?"

"You never know. Narcs plant pot in my pockets sometimes." And then a whole paranoid fantasy spilled out about the CIA, Homeland Security, and the FBI trying to entrap him, his cell phone being tapped and a virus in his computer sending every key stroke to Google. Sometimes he heard their chatter about him leaking out of his cell phone.

It was a difficult meeting with Jake the next day. He tried to minimize the severity of psychotic symptoms I described in Jim – paranoia, delusions, flat affect, and hallucinations. Jake wanted to blame everything on marijuana. Now that he had stopped Jim's use, Jake was sure Jim would continue to improve. I insisted that, while the marijuana had undoubtedly played a role, it was equally possible that Jim had schizophrenia and needed to be treated for this condition as well. Jake understandably found this a difficult diagnosis to accept immediately and said he needed a second opinion. As is my practice, I encouraged him to pursue another opinion, which would either confirm my diagnosis or teach me something I missed. I advised him to be sure that whoever rendered the second opinion was well trained in both marijuana addiction and psychotic disorders.

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Chapter

8

The Impacts of Ongoing Marijuana Use on Adolescent Psychology

Understanding the Journey from Childhood to Adulthood

Adolescence is a distinct and unique phase of life, different from the previously known calm of childhood and the consistency of adulthood that comes later. It is a time of remarkable brain development, expanding physical and cognitive abilities, profound psychological growth, and often explosive hormonally driven physical and emotional transformation. Overlaying marijuana or any other drug on top of adolescent brain and psychological development produces far more intense impacts than marijuana use during adulthood. This chapter looks at facets of psychological development routinely disrupted by excessive marijuana use.

The combined processes of pruning and myelinization necessary for final maturation starts with puberty at the back of the head and gradually advance toward the front.[1] The importance of this uneven maturation process is that the frontal lobes, the most recent evolutionary development in humans and the last portion of the brain to fully mature, is the neurological scaffolding for our executive functions. As a result, abstract thinking, sequencing, prioritization, planning, and judgment are the last mental capacities to fully come on board. Mature frontal lobes permit us to respond with conscious reflection rather than merely reflex reactions. They enable us to view present events within the broader context of our life and to modulate our emotional reactions.

Deborah Yurgelun-Todd at Harvard provided an excellent illustration of changes brought about by the maturation of our frontal lobes when she showed images of fearful and happy faces to children between 8 and 15 years old while performing fMRI.[2] The youngest individuals showed activation by the fearful face only in the amygdala, the seat of our fight-or-flight response. As age increased, activation in the frontal lobes gradually became more prominent. Researchers call this the "frontalization of amygdala function." It is the placing of more "primitive" emotional reactions into a broader cognitive framework. I once saw the reverse of this process in a man who had suffered a frontal lobotomy.

Without the frontal lobes' executive functions to modify his reflex emotions, he misinterpreted a raised fist, meant as a greeting of solidarity, as a hostile threat. He had no broader cognitive context to modify his amygdala's primitive fear reaction and was never able to read social cues accurately.

The adolescent's journey from childhood to adulthood involves the process of progressive frontalization, the coming on line of increasingly powerful executive functions as frontal lobes mature. The pruning and myelinization underlying this maturation are initially rapid, but the final slower development takes many years. How many? Ask car rental companies. They either refuse to rent cars or levy a surcharge for anyone under 26. Their profits depend on drivers with fully adult judgment. In a similar manner, minors given a "life" sentence for serious crimes are generally released at age 26. Of course, 26 is an average age for full brain maturation. Some conditions such as ADHD routinely see an approximately five-year lag in maturation of the frontal lobes. And individual differences abound. The bottom line is that everyone goes through gradual maturation of their brain, with the frontal lobe functions being the last to achieve completion.

The significance of ongoing brain development during adolescence is two-fold. First, the full complement of executive functions required for mature perspective and judgment are often not fully available when the first decisions about drug use are made, and this is especially true for the youngest adolescents. For most people, nicotine (cigarettes or vaping), alcohol, and marijuana are the first drug opportunities encountered. And second, brain structure is more easily compromised the earlier in development disturbances occur.

The onset of more abstract thinking has a profound impact even before its full development. Complexities in the world, and in one's inner life, appear and must be integrated into a changing identity. One is no longer "just a kid," but not yet an adult. The question of where one fits into the world has no clear answer. Some adolescents respond to this challenge with curiosity and enthusiasm. Others become cynical in response to discovering how much hypocrisy permeates the adult world. Some strive toward growth while others contract and reject the adult world. Differences in how children respond to being overtaken by adolescent development result from a mixture of their genetically determined temperament and intelligence, experiences provided by their families and culture, the prevalence of trauma and availability of drugs, to name but a few of the major influences.

I find it easy to understand why many adolescents are attracted to experiencing drugs. It is a heady time of life. A huge number of new experiences become available with puberty and burgeoning frontal lobes. Curiosity is stimulated by both and should be encouraged and channeled in healthy directions, though adults have only limited ability to direct an adolescent's curiosity compared to the influence of their peers. Modelling healthy choices ourselves and living a life of high integrity is the best influence we can provide, but often more difficult than we would like to admit!

There is, however, a very distinct difference between "experimenting" with any drug and "using" it. The motivations between the two are quite different. As I said, adolescence is a time for curiosity and taking risks. Simply driving a car is an exciting risk. Some, but not all, find that driving fast is even more exciting. Wearing a low-cut top, joining a neighborhood pickup basketball game with the big kids, plunging down a black diamond precipice, grinding a skateboard down a long railing or entering a music contest for the first time are all exciting risks. And

roughly 55% of teens are curious enough about marijuana that they take this risk by the time they are seniors in high school.

A far more important question than "Why do teens try marijuana?" is "Why do some continue to use marijuana?" The simplistic answer is that they become addicted, but why do they use enough to become addicted? And are the only adolescents harmed by marijuana the ones who become overtly addicted, or can a teen be negatively impacted by marijuana use that is less than enough to become frankly addicted? The rest of this chapter presents a framework for understanding that the answer to this last question is affirmative. In fact, the seduction of marijuana for adolescents may be even more harmful than its physically addictive potential.

To understand the seductiveness of marijuana and other drugs for adolescents, it is important to explore some of the psychological tasks universally faced during this phase of life and how marijuana seems to successfully substitute for completing these tasks. There are a set of developmental steps nearly everyone has to take during the years between childhood and adulthood. The tasks/challenges teens have in common fall into the following areas:

Identity and Values

The question "Who am I?" is intensely important during adolescence since the simple identity of childhood is stripped away by puberty and rejected by those in a rush to grow up. Centuries ago the question of identity may not have been as difficult to answer. For most people, life was contained in a small geographic area, often one unchanging village, and physical survival demanded far more attention than did psychological development. Individuals generally absorbed their family's identity, largely because so few alternatives were available. Today, however, youth come into contact with influences from around the globe before they enter grade school. The choices of who to be are infinite, and there is plenty of time to try on multiple identities while preparing for adult life. American ethos emphasizes discovering the True Self and not giving in to conformity. As a result, few teens are content simply to adopt their parents' identities.

Our sense of identity is largely determined by the values that guide our lives. We may value physicality and sports, the arts, religion, patriotism/loyalty/belonging, or academics. We may value friends, achievement, liberty, or material wealth. We may value action or feeling, utility or beauty, victory or fair play, power or justice, dominance or cooperativeness, toughness or empathy. Adolescence is when we emerge from being good primarily by minding the rules and start developing more abstract and universal ideas to guide us. It is a time when adult hypocrisy is first recognized, seen as starkly disappointing and aggressively rejected. During adolescence we integrate a sense of identity by adopting personally relevant values and developing our own internal moral compass to differentiate right from wrong. Unfortunately, not all compasses point toward true north.

Peer Group Affiliation

Family members are generally the most important people in a preadolescent's world. The very idea of being more tightly connected to someone outside the family than to blood relatives makes no sense to most young kids. However, with puberty and the upwelling of

sexual energies that are taboo to direct toward family members, the importance of peers increases dramatically.

Allegiances and emotional attachments to others outside the home become intense and even primary. The influence of family fades and is often resisted as a simplistic first pass at developing a separate identity. This creates new problems since adolescents are still dependent upon their parents while feeling a need to be closely affiliated with peers. But which group of peers should they join? Which peers will accept them? The "visible" group? The jocks or the brains? A gang? The nerds or the outcasts? The straights or the stoners? While family generally accepts the adolescent unconditionally, acceptance by peers is not assured, nor is it constant and freely given by peers who are themselves groping for identity and meaningful connections. The question of choosing and being chosen by the "right" group of peers generates much of the stress found in today's teens.

The peer group an adolescent identifies with and the sense of identity he or she adopts are intimately related. As mutual attachments are forged and emotional commitments formed between teens and their friends, their commonality reinforces how they view one another. A tendency to take school seriously, for example, is more likely to become a defining characteristic when shared with others. In the same way, disrespect for parents can be so strongly reinforced within a peer group that teens are embarrassed to feel any affection for parents, much less be willing to display it publicly. Peer groups enhance specific aspects of an adolescent's personality, de-emphasize others and lead people to try out behaviors that they would be less likely to try on their own. These influences can be positive or negative. And none of us has as much influence over which peers our children are attracted to as we might wish.

Sexual Maturation

With the onset of puberty sexual hormones rise up to take control of adolescent bodies, as well as their emotions. No amount of education prepares children for the realities of puberty. Dancing about in front of a mirror like pop stars was just play, while new sensations and swelling in suddenly noticeable breast buds are real. Posturing like the latest sports hero is just fantasy, while growing pubic hair and noticing the voice drop an octave is real. Looking at the other sex, really *looking*, and desiring something that can only be imagined makes it clear that an adolescent is no longer just a kid anymore. Being looked at differently by older boys drives this lesson home even more deeply for girls. Teens suddenly have what every adult has, and it feels good.

Puberty happens at its own pace for every adolescent. How much smoother it would be if everyone experienced the same changes together, like when everyone moved together from grade school to middle school. Instead, a few preteens enter puberty first, and a few enter it last. As arbitrary as each individual's timing is, it nevertheless has a major impact on a teen's life and self-esteem to be either "too soon" or "too late." Being preyed upon, ridiculed, or admired on the basis of sexual development often greatly increases the need for acceptance.

Autonomy and Separation

For adolescents to make new connections outside the family they must complete two intertwined developmental tasks: autonomy and separation. Each child emerges from the womb as more than a combination of qualities from their mother and father. We are each

unique, with characteristics, drives, and urges that differ from both of our parents. Healthy families make room for, honor, and welcome these differences. But even in families that are not threatened by their children's own ways, each child has to discover how to value all of who he or she is. Eventually the world demands that adolescents accept and take responsibility for their individual qualities no matter how much they may differ from their family norm. This is autonomy.

Separation from family is eventually necessary for several reasons. We all must leave home, literally or figuratively, to solidify our sense of self and our ability to take full responsibility for ourselves. We must all prove our competence at navigating the world at large to know, really know deeply, that we have become adults. Only then can we rework the relationship with our parents, adult to adult. We begin living our own lives during adolescence.

Transcendence and Meaning

Finally, teens are often plagued by the need to begin making sense of the world and their lives. I say "plagued" because most of us eventually discover that our childhood understanding of life is no longer acceptable and must be discarded even before we have anything to replace it. As we become able to think abstractly during adolescence, we see more of the complexities of life. But, paradoxically, less and less of the world makes as much sense as it seemed to when we were younger and saw everything in simpler terms. Many, if not most, teens feel betrayed by their confusion – betrayed because they had previously thought parents knew what they are doing all the time and because they had always been assured that everything would be safe and okay. Now they discover that the world contains real injustice and cruelty, with no guarantee good will triumph. Adolescence is a time of immense spiritual challenge for which a great many teens have had inadequate preparation. As a result, many feel adrift, without any clear sense of meaning in their lives.

Youth are often left searching for answers. Is there any significance to life beyond surviving, eating, sleeping, and reproducing? Does it add up to anything more than who gets the most toys before they die? Many teens react strongly when they first see disturbing realities that had been hidden by parents' desire to protect them and by their own inability to think abstractly. Some become cynical and bitter. Others wonder where justice can be found. And most long for some of the certainty and clarity they had only a few short years ago. Many hope that getting into adult life will bring some answers to the difficult questions that stole their last remnants of childhood. Adolescents feel a strong drive to transcend their current life – emotionally, psychologically, physically, and spiritually. This drive motivates maturity, but can also be siphoned off into seductive detours that lead to blind alleys.

Onset of Marijuana Use

The initial experimentation with marijuana can be a watershed moment in a teen's life. Despite all the anti-drug messages received in school and at home, many teens (and preteens) decide to risk getting high soon after the opportunity first presents itself. This single act is a clear step away from the path prescribed by most parents. Lighting up is an act of direct disobedience in families where the importance of not using drugs has been emphasized. (I am ignoring for the moment those parents who introduce their children to using marijuana, either directly or by carelessly leaving their stash unhidden.) Trying marijuana for the first time is also an act of self-assertion. Teens who weigh the issue

usually focus on whether they will be caught rather than whether pot will harm them. At this point, teens do not doubt that they are charting their own course. A new truth is being adopted. They are claiming their freedom, defying their parents, and no one can stop them. That is a fact and a remarkable discovery. The result is often an experience that seems so benign, fun, and fascinating that cautions and well-meaning warnings by adults suddenly seem unbelievably stupid and hypocritical.

An adolescent's decision to smoke marijuana is often seen very differently by the two sides – parents and child. The disparity in how each perceives this moment is important to understand because it forms the framework for a lot of failed prevention programs and a lot of unsuccessful family conversations/arguments. Chemical dependence trainer David Wilmes asked both parents and teens why they believe kids take drugs and found some interesting differences.[3] Adults gave the following reasons that kids use drugs:

- *School*: "Can't those teachers see what's going on? Don't the kids get any supervision?"
- *Other parents*: "Well, what can you expect from a home like that?"
- *Peer group*: "My kid never had any problems until he/she got in with that bunch."
- *Pushers and alcohol/tobacco sales*: "Put the dealers in jail and close up sleazy alcohol stores."
- *Media*: "What can you expect when movies and the Internet portray that it's cool to use drugs?"
- *Police*: "If the cops were on the ball, they'd pick up those kids the first time they got out of line."
- *Role models*: "Those rock stars and professional athletes are all into drugs. And these are the people our kids want to imitate."

These reasons generally point to external factors. Perhaps parents are reluctant to believe that their children would willfully defy them unless others were pressuring them. Parents tend to place great emphasis on peer pressure as the cause of adolescent drug use. As a result, drug prevention programs are heavily weighted toward helping kids resist peer pressure. This perspective is guided by the belief that drug pushers are lurking around every corner waiting for our kids. Without these pushers, our children would follow their better instincts and mind their parents.

Of course all these factors play some role, but teens tell a different story. When asked why they take drugs, teens give the following reasons:

- "I wanted to see how I'd feel."
- "I wanted to be part of the group."
- "I didn't want to be a nerd."
- "I just wanted to have some fun."
- "I like to take risks."
- "I'm no baby. I can make up my own mind."
- "I like to experiment with new things."
- "I wanted to feel grown up."

Unlike adults' perspective, the adolescents' reasons are more internal. While teens may be underestimating the presence and power of peer pressure, they also own responsibility for their decisions to a greater degree than parents seem willing to give them credit for. This is completely consistent with the need teenagers have to take control of

their lives. They are intrigued by the wide world, including sometimes by what the experience of being high would feel like, and they even enjoy the risk it might entail. No one thinks it odd when a teen courts the risk of rock climbing, sailboarding, joining the military, fast driving, or hanging with a gang member. These risky behaviors may make us nervous, but we see them as normal adolescent behavior, part of defining their limits for themselves. The impulse to experiment with marijuana has the same lure as other risky choices.

Understanding adolescents' perspective is an important step to being able to communicate with teens. The temptations that attract them and the desires resident in their hearts form part of the cutting edge by which they learn their true identity. Adolescence is an important time for coming to terms with adult desires while still constrained by the limitations of adolescent resources. Teens are teaching us something important when they list their internal reasons for using drugs. As parents, however, we are often nervous when we see consequential decisions being made by children who have often developed more freedom than discernment. Despite parents' wishes, one simple, available, and relatively passive avenue adolescents have for exploring their newfound freedom is through experimenting with marijuana, alcohol, and other drugs.

Marijuana confuses adolescents by seeming to accelerate maturation while actually delaying it. With one puff on a joint, the question "Who am I?" develops new answers even before getting high. "I am a risk taker. I am free from old constraints. I am not the child my parents still think I am." **Autonomy**. A line has been crossed – a line between them and us. Now an adolescent is one of "them," fully distinguished from the person he or she was only a few moments before. The excitement of the moment can be truly electrifying. A whole new facet to one's identity is created and a new peer group is joined. For many teens the experience is tantamount to joining a secret society, complete with informal code words, insider expressions, and double meanings. Even straight experience seems altered as the new initiate walks through the next few days with an inner knowledge that no one else suspects. Parents, teachers, and other naïve adults do not see the new truth. For some, maintaining an appearance of being unchanged can become a delicious deception. For once it is profoundly clear that the outside world does not know who the adolescent *really* is. The act of using marijuana substitutes for developing a more substantial sense of identity. **Separation**. Others separate themselves more overtly, seemingly as a matter of integrity, by adopting stoner regalia, sporting Bob Marley tee shirts and listening to reggae to declare their conversion publicly.

The first experiences with marijuana are pleasant for most people, although a small percentage immediately dislike pot because they become anxious and feel a loss of control, paranoia, and even panic. For most, however, what had been a source of apprehension and excitement only a few moments before the first inhalation ("What will getting high really be like for me?") quickly becomes a new playground, often filled with raucous laughter and silliness. The experience of getting high ends up being just plain fun for most, which suddenly throws all the dire warnings they had heard about marijuana into serious doubt. The marijuana culture carries a set of values that are easily adopted by new users. Anyone seen as being anti-pot is now considered uninformed and ignorant, oppressive, and hypocritical. Many adolescents feel adults have lied to them about drugs, and this feeling is inflamed by the new peer group they have entered. Stoners know the "truth" about marijuana from their own

direct experience. Anyone who disparages weed is not to be trusted any more than you would trust someone who says the sky is green, not blue. The immediate acceptance into this new peer group brings a strong sense of belonging and at the same time can drive a wedge between the teen and non-users. The process of withdrawing from family for the purpose of hiding and protecting marijuana use, or openly advertising your conversion, has begun. **Independence**.

True autonomy requires developing the internal capacity to take responsibility for oneself and the consequences of one's decisions. The pseudo autonomy of being high is less about being able to take care of oneself and more about being able to cast off parental control. Few adolescent marijuana users see that parental controls remain central to their identity by virtue of defining themselves as rejecters of parental authority. Getting high creates an impression for many teens that they are free, independent spirits, thinking and acting for themselves. No one can tell them what to do, and each joint they light up seems to confirm their freedom.

This simulacrum of independence gets played out in several different ways. Some adolescents overtly scoff at any attempts to corral them. They blatantly disobey parents, ignore school authorities, and come into conflict with police and the juvenile justice system. Throughout this process they become progressively more "radicalized." As frustrated parents yell threats and try to clamp down with rigid control, some teens feel increasingly justified in their alienation. As defeated school officials impose expulsions, adolescents can feel cast aside by adults. As police bring the often clumsy, heavy hand of the law down upon them, marijuana users become more outraged at the hypocrisy and injustice of a system that wants to punish them while ignoring how often drunken parents get away with neglecting their children. Those who most directly and overtly reject straight society are most punished and, in a real sense, the most honest about their feelings, but they are also usually the least understood.

On the other end of the spectrum are those teens who quietly develop devotion to smoking marijuana without revealing a trace of their secret life. They maintain their grades. They maintain their behavior. But they have gone underground psychologically. They operate with an illusion of independence as they live progressively more in disguise. These kids are the hardest to really know. Naturally tending more toward introspection than toward action, they are often attracted to the sense of transcendence offered by the "magical" powers of marijuana.

Michael Pollan, in his enjoyable book *The Botany of Desire*, points out that transcendence "depends for its effect on losing oneself in the moment."[4] Marijuana's tendency to disrupt memory, slow the perception of time, and stimulate awe mimics transcendence. To some people this can be disturbing. They become uncomfortable with the mild disorientation created by the mental discontinuities that occur. Others find the experience hilarious. They enjoy being bumped "out of the box" of their normal patterns of thinking and believe that the experience enhances creativity. While most of the "amazing" ideas that appear while high are neither practical nor well remembered in the cold light of the next morning, the astronomer Carl Sagan, in his Internet article "Mr. X," wrote that he benefited from occasional visits to the altered consciousness created by marijuana.[5] In his words, "If I write the insight down or tell it to someone, then I can remember it with no assistance the following morning; but if I merely say to myself that I must make an effort to remember, I never do."

A wide range of cultures over millennia have incorporated marijuana into spiritual practices. When THC stimulates the amygdala, the combination of intensified sensory experience, virtual novelty, and being taken out of day-to-day experience gives people a taste of transcendence without any spiritual effort. Adolescents can quickly become enthralled by the experience of being high, away from their humdrum lives, away from the challenges and responsibilities of school, family, and an uncertain future. The strange world of high possibilities can be entrancing. This is not genuine spirituality, but it does kick people out of their normal ways of relating to the world. It does reveal that a universe of other possibilities exists, although it does not help to *realize* any of these possibilities. To adolescents, who lack the life experience useful for resisting such temptations, or who are genetically prone toward addiction, marijuana may seem to be the key that unlocks their way into a different world. They make the common error that Alan Watts in *The Wisdom of Insecurity* described as seeing the finger pointing the way and then sucking it for comfort rather than following the direction it points.[6] There is a universe of possibilities open to adolescents, and this is a good thing to know and believe. But the task is to enter that world in reality, not merely to experience it in fantasy.

The effect of marijuana during the years of adolescent development is all too often to delay and distort psychological, emotional, social, and spiritual maturation. The younger a teen is when beginning marijuana use, the more the resulting developmental delays and distortions may cascade through his or her personality, building a momentum that can extend the negative consequences far into the future. When adulthood is built on a poor foundation, the effects can reverberate for a lifetime.

The earlier an adolescent begins smoking marijuana, the higher the risk that he or she becomes enthralled and seduced by the experience. For a small, but not insubstantial, minority seduction soon gives way to devotion, and addiction is not far behind. To be addicted (from the Latin *ad dictare*) means to address one's entire life to that substance – to make its use the central organizing principle of your day. Everything else in one's world and in one's psychology, is subordinate to obtaining, using, or recovering from using the drug. Not all people are equally susceptible to being seduced or developing addiction to marijuana. Some run a much higher risk for genetic, family, or environmental reasons. But everyone who exposes themselves to marijuana exposes themselves to at least some element of risk. The crux of the matter revolves around how we manage the risks we take.

Any drug can serve as a vehicle for adolescents' drive for identity, autonomy, and separation. Alcohol still heads the list, but marijuana may be uniquely qualified. The historical impact of the 1960s rebellion against traditional America is still strong. In addition, marijuana is pharmacologically well positioned to seduce adolescents. It produces virtually no hangover and no messy vomiting. The impact of chronic use is relatively subtle and therefore easy to hide, ignore, and rationalize. And there is no possibility of a fatal overdose.

Adolescent development, when successful, is a time of increasing empowerment – a time of coming into your own as a competent young adult. The first blush of empowerment for many, maybe most, adolescents is experienced as a sense of invulnerability. As a result, risk is often minimized and the possibility of negative consequences is misjudged. Adolescents live NIMBY lives. They know fast driving kills – but "not in my back yard," not me. Prevention efforts to reduce teen tobacco use by education about

lung cancer, emphysema, and heart disease were not very useful. The future is still too distant a reality for adolescents (as it is for many adults as well). The rate of cigarette use fell among teens only after smoking became an undesirable adult activity and tobacco companies were demonized.

Nancy Reagan raised the perception of risk with her "Just Say No" campaign and marijuana use among adolescents fell – temporarily. When her anti-drug messages stopped and adolescents were left with only their relatively benign and enjoyable experience of marijuana, perceived risk plummeted and use rose again. As an eternal optimist about the eventual power of science, I believe prevention strategies based on discoveries about the impact of chronic marijuana use on brain structure, cognition, emotion, and psychology, with an emphasis on harms to adolescents are the best hope for protecting youth. Once these facts are understood, the true risks of marijuana, and especially of the early onset of marijuana use, can be faced realistically, squarely, and without either exaggeration or denial.

Chris

Martha and Richard saw me out of concern for their 16-year-old son, Chris. He had been an excellent student and voracious reader up until the summer before 10th grade, when his marijuana use broke out of weekends and began invading daily life. His grades soon slid, video games replaced books, and he sometimes disappeared for a couple days without warning or explanation. His parents were so terrified they would never see him again that they welcomed him with forgiving arms when he returned. Despite being given extraordinary freedom, against his parents' better judgment, Chris constantly berated them for trying to control his life. With summer vacation approaching, his parents sought advice on how to encourage their son to reduce his marijuana use and reignite his reading habit. Their plan was to reward Chris with $20 for every book he finished. After reviewing the role of our reward center in the addictive process, I explained that the motivation for marijuana's reward was greater than anything else money could buy, making it likely that any financial reward would only be used to buy more pot. A brief history found no evidence of oppositional-defiant behavior before the onset of marijuana use. Chris's relationship with his siblings had always been good, even kind. The only family psychopathology seemed to be a strong history of addiction in Chris's grandparents, aunts, and uncles.

When Chris slouched into my office he plopped down in my chair, which was obviously bigger than the others. I remained standing during the initial portion of the session, wondering if he would say anything to acknowledge sitting in my place.

"You look unhappy."

"I'm not at all happy being made to come here."

"How can anyone make you come?"

"I won't get any allowance this week if I don't."

"I'm sure that pisses you off." He started what was probably going to be a rant about his fascist parents, but I interrupted him. "I assume you need the money."

He sat sullen and quiet, then looked up at me and asked, "You going to stand the whole time?"

"You're in my seat." This comment was designed to set the tone for our conversation, giving him information without telling him what to do with it. He looked around and then reluctantly moved over to one of the other chairs. Before either of us were settled

I said, "I think you are unhappy about a lot more than just having to come here. I'm interested."

"You ever have parents who tried to control you all the time? Mine don't trust me for anything. They want to know every move I make, every friend, every time I blow my nose or wipe my ass. They don't understand I don't need them. I take care of myself OK."

"You don't need them."

"Nah. They should get me an apartment and let me live on my own if they want me to be happy."

"How did you get so independent? Most kids your age would be scared to live on their own."

"Most haven't handled what I already have."

"Really? You're proud of yourself."

"Damn straight. I've stared down people older than I am when a dope deal went bad. And I know how to deal myself."

I knew Chris was mostly bragging, but it was all in service of maintaining his self-image – independent, accomplished, capable, no longer a kid.

"Can I tell you what I've learned about you already?"

He looked torn between wanting to dismiss me and curiosity about what I might say. I think he decided to listen in order to let me hang myself. "Sure," he said insolently.

"You value self-reliance. Good, that's what we want young people to learn." I kept talking rapidly in order to prevent his interrupting. "You value freedom and adventure. You value accomplishment. You are a proud young man. You already see yourself as a man of action and you want to succeed . . . Am I right so far?"

"Pretty much, but I don't know if you really believe what you say."

"It doesn't matter what I believe if it's true. So how can we help you achieve even more of these things?"

"I don't need your help."

"You may be right, but a wise man always uses whatever help is available to get what he wants."

I suggested that Martha and Richard change their perspective from what Chris was not doing to what he saw himself trying to accomplish (misguided though his means might be), and change their strategy from bribing Chris into healthier behavior to taking action to assure the THC blunting motivation for anything else was removed. Since they were fortunate enough to have resources, I referred them to an educational consultant who could recommend a series of adventure camps, a vision quest, and therapeutic wilderness programs to fill the summer instead of allowing Chris to hang out with his using buddies and pretending to read a couple books each week to feed his addiction. The consultant would be careful to choose programs that closely monitored any drug use with testing, if needed. With luck Chris would find the programs exciting enough to cooperate and perhaps he would be willing to see a therapist upon returning or to enter a treatment program if he relapsed. If the physical challenges, time away from home, and vacation from marijuana was not sufficient to turn things around, his parents could entertain the possibility of having him complete high school at a therapeutic boarding school.

Notes

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3. D. Wilmes. *Parenting for Prevention*, Hazelden Publishing, 1995.

4. M. Pollan. *The Botany of Desire*, Random House, 2002.

5. Mr. X by Carl Sagan was written in 1969 for publication in *Marihuana Reconsidered*, 1971. http://marijuana-uses.com/mr-x/ (Accessed March 22, 2019.)

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Chapter

9 Secondhand Marijuana: Prenatal Cannabis Exposure

Despite very active marijuana research worldwide, data regarding the impact of in utero exposure to marijuana lag behind other areas of interest for understandable reasons. The expense, complexity, and commitment required for long-term prospective longitudinal studies make them daunting endeavors. As a result, this chapter is shorter than we might wish, and the conclusions more tentative. At the same time, the topic of lifelong impacts of fetal exposure to secondhand marijuana on neurodevelopment might ultimately be of paramount importance.

Marijuana use during pregnancy is common.[1] A 2001 nationwide study in the U.S. found THC in 7.2% of infants' meconium (the first discharge from a newborn's bowels)[2] and a Scottish study in 2002 found 13.25% of meconium positive for THC and/or its metabolites.[3] In 2016, 4.9% of pregnant women between 15 and 44 years old reported marijuana use in the past month compared to 11% of non-pregnant women in the same age group. Women at the younger end of this spectrum were more likely to report past month use – 8.5% of 18–25-year-olds versus 3.3% of 26–44-year-olds.[4] Unfortunately, up to 28% of high-risk pregnant populations (urban, young, socio-economically disadvantaged) use marijuana.[5,6,7] Although the 2012 National Survey of Drug Use and Health (NSDUH) reported marijuana use decreased over the three trimesters, from 9.0%, to 4.8%, to 2.4%,[8] other studies have found that 48–60% of cannabis users continue their use during pregnancy, believing that it is safer to use than tobacco.[9,10,11]

Smoking or vaping marijuana leads to THC concentrations in the fetus that are about one third that of the mother.[12,13] In the face of this transfer of THC across the placenta to fetal blood, one study found that 51% of women using marijuana during pregnancy cited relief of nausea and vomiting as the reason (92% of whom reported its effectiveness, though no controls were included in the study).[14]

A note of caution needs to be raised regarding using marijuana to treat refractory nausea and vomiting. With increased marijuana use nationwide has come recognition of Cannabinoid Hyperemesis Syndrome (CHS), characterized by at least weekly marijuana use, cyclic nausea and vomiting, abdominal pain, and frequent hot bathing, which temporarily relieves symptoms. Emergency room treatment consists of IV fluid replacement, antiemetic (e.g., haloperidol), capsaicin cream, and recommendation to discontinue marijuana use. Since CHS has been reported during pregnancy, care must be taken to consider this possibility in marijuana-using pregnant patients with refractory "morning sickness."[15,16,17,18]

Despite the potentially scary statistics outlined above, it remains unclear how seriously harmful prenatal exposure to marijuana may be. The primary initial impact is lower birth weight. A tertiary teaching hospital reported that infants born to mothers positive for only THC at both their first prenatal visit and delivery had a median birth weight of 2925 g versus 3235 g for those with mothers who tested negative. Maternal use during pregnancy results in more pronounced growth restriction than tobacco use.[19] There was no clinically relevant difference in gestational age at birth.[20]

Unfortunately, hard data regarding long-term consequences of prenatal exposure are still scant for three important reasons. First, fetuses are almost certainly being exposed to much higher THC concentration marijuana today than when the studies began. Second, there are so very many confounding variables, including other drug, alcohol, and tobacco use, that it is extremely difficult to tease out what effect is directly related to marijuana. Third, the only truly reliable data come from long-term studies that start during gestation, when maternal marijuana use can be accurately documented, and that last for at least a couple decades of an offspring's life. Few people can remember their marijuana use 3, 6, and 10 years earlier when their child undergoes cognitive testing. Long-term studies are expensive, require a committed team of investigators and are therefore rare. Only three such studies currently provide useful data.

The Ottawa Prenatal Prospective Study (OPPS) beginning in 1978 tracked a low-risk, European–American, middle-class sample of pregnant women.[21] The Maternal Health Practices and Child Development Study (MHPCD) started in 1982 and focused on high-risk pregnant women of mixed ethnicity with low socioeconomic status in Pittsburgh, Pennsylvania. And the Generation R study is following a cohort born between 2002–2006 in Rotterdam, Netherlands.[22] As a result of the variation in populations and focus of the studies, results cannot be compared and few of their results have been replicated, an absolute necessity for any scientific finding. Their results can be divided into immediate impacts observable at birth and longer-term impacts that become apparent only later in a child's life.

Initial Impacts of Prenatal Marijuana Exposure

The THC in marijuana has not been shown to cause obvious birth defects in humans or laboratory animals, though the potential for subtle neurological defects will be discussed in the following section. Early studies reported that daily marijuana users experience an increased rate of precipitated labor and shortened gestation by one week, which is dose-related.[23,24] Immediate newborn effects were described as increased tremors, exaggerated startle, a high-pitched cry, and abnormal sleep cycling.[25,26,27,28] These effects are consistent with the symptoms of marijuana withdrawal. However, more recent studies designed to disentangle the effects of marijuana from other factors, including tobacco,

alcohol, and other drugs, have found no independent adverse effects from marijuana, though the combination of marijuana and tobacco is clearly problematic.[29,30] Despite limited and inconsistent data, the American Academy of Pediatrics concludes that "the evidence from the available research studies indicate reason for concern, particularly in fetal growth and early neonatal behaviors."[31]

The National Academies of Sciences, Engineering, and Medicine likewise found in its exhaustive 2017 report that, while smoking marijuana is linked to lower birth weight, the relationship to other pregnancy and childhood outcomes is unclear.[32] However, the report raised concern that "endocannabinoids play roles in a broad array of critical neurodevelopmental processes, from early neural stem cell survival and proliferation to the migration and differentiation of . . . [neurons] as well as neuronal connectivity and synaptic function."[33,34]

The embryonic endocannabinoid system is excellently positioned, physically and temporally, to impact very early brain development. The entire system – receptors, anandamide, 2-AG, and the enzymatic machinery for their synthesis and breakdown – exists within ~16 days after fertilization, prior to emergence of the nervous system.[35,36] The neural tube, which forms the precursor of the central nervous system, does not even close until ~day 28. Thereafter endocannabinoids play a significant role throughout neural development, the proper formation of neural circuitry early in brain development, "including the genesis and migration of neurons, the outgrowth of their axons and dendrites, and axonal pathfinding."[37,38] Given the central and pervasive role of endocannabinoids in neurodevelopment, most especially prenatally, it makes sense to look closely for potential impacts of increased cannabinoid activation potentially produced by maternal marijuana use.

Long-Term Impacts of Prenatal Marijuana Exposure

Results from both the OPPS and the MHPCD suggest significant adverse neurologic effects in children, adolescents, and young adults with prenatal marijuana exposure, including impaired mental development at nine months, impaired verbal, abstract, visual, and quantitative reasoning, and impaired short-term memory at three years, impaired memory and verbal development at four years and impaired sustained attention and increased impulsivity and hyperactivity at six years.[39,40,41,42,43]

At the point that higher cognitive abilities begin to mature and can be more reliably tested, adverse consequences include increased hyperactivity, impulsivity, and inattention at 10 years and impaired executive function and visual problem solving at 9–12 years.[44,45,46] Adverse consequences in adolescence/young adulthood include problems with attention, problem solving, visual integration, and analytic skills requiring sustained attention seen between 13 and 16 years old.[47,48,49]

Functional MRIs from ages 18 through 22 years during working memory and executive function tasks (visual-spatial memory, go/no-go and Stroop) reveal significantly less activity in the frontal lobes and compensatory increased neural activity in multiple other areas of cortex.[50,51] In her 2016 review article, OPPS researcher Andra Smith offered the following summary:

> Although both [the prenatally exposed and non-exposed] groups were able to successfully perform the fMRI tasks, the increased activity of the prenatally exposed group suggests the

> need for a compensatory response whereby either additional brain regions are required to perform the tasks or more activity in typically activated regions is necessary. It is possible that the two groups had different strategic approaches to perform the tasks, however, this too is suggestive of a required compensation . . .[52]

Results of her fMRI study of adolescents prenatally exposed to marijuana appear similar to the compensatory cortical activation seen in adolescents using marijuana studied by Susan Tapert at University of Califoria San Diego (Chapter 6).

Psychological and behavioral problems were also reported by both the OPPS and MHPCD studies. Higher rates of problematic externalizing behavior as early as age 6 and depressive symptoms as early as age 10 have been reported.[53,54,55,56] An increased risk of cigarette and marijuana use is seen between 14 and 21 years and in early adulthood, though parental modelling may well account for this early onset of use.[57,58,59] There is even some indication of increased risk of young adult psychosis.[60]

It must be stressed that the above mélange of findings, while clearly suggestive of potentially important impacts of prenatal exposure to marijuana, absolutely requires further study before a consistent, replicated pattern of effects is well described. At some future time, we may look back on this small cadre of concerned researchers producing these early studies as pioneers who saw the obvious before it was generally recognized. The data are not hard enough yet, but strong support for the clinical effects outlined above has been developing in the basic science laboratories of animal and molecular researchers. While rat studies do not always generalize to humans, they do reinforce emerging patterns regarding the impacts of prenatal marijuana exposure.

Fetal Brain Development

Every human begins as a single hybrid cell. Most of this cell consists of the maternal egg, with the addition of 24 chromosomes from the male's sperm. Together they comprise the ultimate stem cell. As the fertilized egg divides, its successors differentiate into every variety of cell contained in our body – bone cells, immune cells, blood cells, cardiac pacemaker cells, insulin producing, light detecting, and hair growing cells. The panoply is nearly beyond comprehension.

Nowhere is the pluripotentiality of cellular development more spellbinding than in the fetal brain, which relies on three crucial self-organizing events: (1) the differentiation of protoneurons capable of proliferating into all the cells in our brain, (2) the migration of neurons to specific locations, and (3) functional synaptic connections between neurons, both near to and far from each other. Wow! And we now know that our CB1 receptors and endocannabinoids, anandamide and 2-AG, are intimately involved in directing all three stages of fetal brain construction.

There are 200 times the amount of 2-AG than anandamide in the adult brain, but 1000 times as much in the fetal brain. Delicate balances between the two endocannabinoids, the enzymes that synthesize and degrade each, and the transient appearances of CB1 receptors in white matter are responsible for directing the growth of axons.[61,62] At the leading edge of each growing axon is a growth cone. Microtubules that form the internal skeleton of the axon undergo rapid assembly in the growth cone, pushing the axon out toward its intended destination. Axons do not "know" their destination any more than any of us do when we have lost our cell phone and call it to be guided by its ringing. We move toward the louder rings, eventually finding the phone in a laundry

basket or under a newspaper. In an analogous way, bundles of growing axons are guided along a chemical gradient until they meet a neuron cell body, where they stop growing and develop synaptic connections. When THC is introduced during this critical developmental period, it displaces our endocannabinoids from the CB1 receptors on microtubules guiding axon growth, interrupting the delicate molecular interplay and dampening their signaling efficacy. Microtubules branch where they should not. The end result is diminished axonal integrity. As described in Chapter 6, Staci Gruber used Diffusion Tensor Imaging to reveal the relationship between reduced white matter fiber tract integrity in the frontal lobe and higher impulsivity scores in marijuana users.[63]

In 2014, Giuseppe Tortoriello and his Swedish, American, Finnish, English, Austrian, and German team of researchers reported a critical leap between bench research in molecular laboratories and human fetal brain development.[64] While research on THC's disruption of microtubules in axonal growth cones was initially discovered in mice, Tortoriello compared the distribution and density of a protein necessary for microtubule elongation (SCG10) in the hippocampi of electively aborted second trimester human fetuses that had been exposed prenatally to marijuana. The production of SCG10 was reduced by 20% in marijuana-exposed fetuses. These results identified a specific molecular target for THC in the fetal brain that directly and permanently impairs the wiring in developing neuronal networks. The damage was specific to THC, since rat studies show that elevating anandamide and 2-AG, our brain's natural cannabinoids, does not reproduce the full spectrum of responses observed with THC.[65]

Prenatal marijuana exposure impairs the efficiency of information transfer between the two hemispheres of our brain through the corpus callosum, the large bidirectional band of axons interconnecting the two hemispheres. This impairment was demonstrated by asking 16-year-olds to maneuver a cursor through different angled target paths using a response box with two knobs, similar to the Etch-a-Sketch toy.[66] Bimanual coordination tasks measure the efficiency with which information is exchanged between the cerebral hemispheres. Both processing speed and coordination between the two hemispheres were decreased in individuals with prenatal marijuana exposure compared to controls.

Tortoriello's discovery of THC's direct impact on fetal brain development was not the first such finding. As early as 2004, joint Swedish and American researchers looked at the impact of prenatal exposure to marijuana on the density of messenger RNA needed to synthesize dopamine receptors in an area of the amygdala known to play an important role in brain circuitry processing reward, motivation, emotion, and cognition. They found a 54% reduction between amygdala dopamine receptor RNA levels in midgestational fetuses with prenatal marijuana exposure compared to controls.[67] The degree of reduction was directly related to the amount of maternal marijuana use. Of particular interest was the fact that male, but not female, fetuses accounted for most of the reduction. This gender difference in dopamine receptor RNA levels fits a pattern of greater decreases in attention, learning, and memory after prenatal marijuana exposure in males than in females.[68,69,70]

Breastfeeding and Marijuana Use

Of all past and current marijuana users in Colorado, where marijuana is legal, 18% used while breastfeeding.[71] Because cannabinoids are fat soluble, THC enters breast milk at

a level that is approximately 10% that found in the mother's blood.[72] Beyond this data, studies of the impact of marijuana use during lactation on infant behavior and development is far too limited to draw any reliable conclusions, particularly since most women using marijuana during lactation also used during pregnancy, and heavier levels of marijuana use are more often accompanied by greater levels of tobacco, alcohol, and other drug use.

Pragmatic Clinical Advice

The American Academy of Pediatrics (AAP) and the American College of Obstetrics and Gynecology (ACOG) have both issued reports on the effects of prenatal exposure to marijuana after carefully reviewing the medical-scientific literature. Both medical specialties issued prudent cautions against marijuana use during pregnancy – the same general cautions given against using any unnecessary drug or medication. In the words of the AAP:

> Women who are considering becoming pregnant or who are of reproductive age . . . particularly adolescents and young adult women . . . need to be informed about the lack of definitive research and counseled about the current concerns regarding potential adverse effects of THC use on the woman and on fetal, infant, and child development; . . . marijuana should not be used during pregnancy.[73]

And the ACOG recommends, "Pregnant women or women contemplating pregnancy should be encouraged to discontinue use of marijuana for medicinal purposes in favor of an alternative therapy for which there are better pregnancy-specific safety data."[74]

The bottom line remains that, while the impacts of fetal exposure to marijuana through the mother's use, especially the delayed long-term impacts, are still to be determined, caution is advised. I see the field as still being in the early stages of potentially important discoveries. I say this because of the patterns underlying these preliminary findings. From the molecular level, to the structural level, animal studies, human fetal to behavioral, and developing adolescent studies, there is coherence to what science is discovering. Just as it took many years to prove to scientific certainty what everyone already knew about tobacco causing cancer, it will require many more years of research to clarify and confirm the exact nature of adverse impacts from prenatal exposure to marijuana. But I have no doubt that, at some future point, the risk of using marijuana while pregnant will be seen as obviously unacceptable. In the formal prose typical of scientific literature, Tortoriello concluded, "irrespective of the legal status of cannabis, caution must be exercised to hinder fetal cannabis exposure due to its unequivocal impact on the establishment of synaptic connectivity in neuronal networks underpinning memory encoding, cognition, and executive skills."[75] Simple translation – you should protect your baby against unnecessary risks.

Some people would probably like to make marijuana use illegal during pregnancy; but, of course, it already is illegal in most places and this has not eliminated the problem. Making pregnant marijuana users criminals only drives people underground and away from treatment. Living in a society that protects both liberty and privacy complicates drug policy, as we shall see in Chapters 14 and 15. For the time being, we need to acknowledge our lack of scientific certainty and continue funding more and better long-term studies of inter-uterine marijuana exposure.

Unintended Pediatric Exposure

When parents fail to secure their marijuana products, whether recreational or medical, young children are inadvertently exposed to another form of secondhand marijuana – accidental ingestion. With decriminalization, poison control centers have reported an increased frequency of primarily edible marijuana ingestion by children (median age ranging from 1.5 to 2.0 years).[76,77] Hospital emergency departments in France and the state of Colorado report similar increases in visits by children with marijuana ingestion.[78,79] A recent literature review reported that lethargy was the most common presenting sign (71%) followed by unsteady gait (ataxia, 14%). Rapid heart rate, enlarged pupils, loss of muscle tone, and confusion were also commonly observed. Acute marijuana toxicity requires only supportive care.[80] Depending on the dose ingested, the child may recover after several hours of observation but may require admission to the hospital, with 18% to the pediatric intensive care unit and 6% requiring intubation.[81] No studies of the long-term impact of childhood acute exposure to marijuana are currently available. A website posted by Children's Hospital Colorado emphasizes the importance of prevention by safe, secure, preferably locked storage of all marijuana products.[82] Although childhood ingestion of marijuana products is relatively rare, its incidence is increasing, serious medical consequences can occur, and it is undoubtedly entirely preventable.

Wendy

Northern California Kaiser Permanente's Early Start Program is a perinatal substance abuse program integrated into the obstetrics clinic as part of prenatal care. I imagine thousands of conversations similar to the following:

Wendy, 26 years old, agreed to a urine drug screen and was positive for a low level of THC, which she did not consider to be a drug. Nevertheless, she also agreed to speak with one of the counselors to assure the clinic she was drug free.

"I understand this is your first pregnancy."

Wendy smiles unabashedly. "Yes, it is."

"You look very happy to be pregnant."

"I am, really happy. I've been dreaming about this since I was a little girl."

"A dream come true. Very good. How far along are you?"

"About 10 weeks."

"And how are you doing?"

"Oh, I'm doing fine. Not too tired, excited. Just a bit of morning sickness."

"How is the baby doing?"

She laughed, almost a giggle. "It's so cool to have you call it a baby. OK, I guess. As far as we can tell. That's why I'm here, to be sure."

"It's always nice when I meet someone who wants to take good care of their baby right from the start."

"You bet. I want to do everything I can to keep it healthy."

"Taking vitamins?"

"Every day."

"Cut back on caffeine?"

"Yep"

"Good. Sounds like you don't want to expose your baby to anything that could even possibly be harmful."

"No, ma'am."

"Are you needing to take anything for the morning sickness?"

"It's not that bad usually. Maybe a hit of marijuana once or twice when I thought I might throw up."

"Did it work?"

She shrugged her shoulder. "I guess. I didn't throw up."

"Good. Have you talked to your doctor about the morning sickness?"

"No. She didn't ask."

"I want to encourage you to talk to the doctor and get her recommendations. There are different medicines to help nausea and vomiting. We want your doctor to choose the safest one."

"I don't want to take any pills. They all have side effects and who knows if they are really safe for my baby?"

"Precisely. You are right not to expose your baby to anything that hasn't been proven safe."

"Well, I'm sure pot's safe. It's just an organic herb."

"Organic is good. But I'm not sure that proves it's safe for your baby. There have been a few studies that followed babies for 20 years after their mother's smoked marijuana during pregnancy and the children sometimes have trouble with learning and concentration."

Wendy looked shocked, disbelieving, and worried all at the same time. "They must have been smoking every day. I've only done a little a couple of times."

"That's great that you have limited it that much because we aren't certain yet what amount is safe, if any. Better safe than sorry, right? I think you are doing very well. I just want to suggest you check with your doctor before taking anything again for the morning sickness."

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Chapter

10 Cannabinoid-Based Medication

Background

Marijuana became legal again as a medication in the U.S. when California voters passed the Compassionate Use Act of 1996. I say "again" because a surge in use of *Cannabis indica* elixirs followed the 1839 publication of a paper by W. B. O'Shaugnessy, a British physician serving in India. Indian physicians had taught him that cannabis relieved the pain of rheumatism in an era before aspirin and opiates, stopped infant convulsions, and quieted the horrible muscle spasms of tetanus. Marijuana tinctures and elixirs quickly became an American and European "superstar."[1] Herb museums contain many examples of this era, such as a Parke, Davis & Co one-ounce bottle of powdered cannabis extract available over the counter.[2]

Although the recreational use of marijuana became illegal in the U.S. in 1937, cannabis tinctures remained on the U.S. pharmacopoeia until 1942. And so 1996 saw the *return* of cannabis as a legitimate medication after 54 years. However, California legalized the medicinal use of marijuana itself – the smokable bud – in addition to tinctures. My colleague, Dr. Peter Banys, calls this brilliant tactic by marijuana advocates "the greatest Trojan Horse since Troy." An incongruous group of alternative medicine advocates, anti-Drug War warriors, civil libertarians, entrepreneurs, marijuana policy reformers, cancer patients, and marijuana devotees worked to pass the Compassionate Use Act and thereby initiated liberalization of marijuana laws in America. Medical marijuana became the camel's nose under the tent, eventually leading 32 more states to follow suit by the beginning of 2019, and legalization of recreational marijuana followed in eight states. Unfortunately, the conflation of marijuana and cannabinoid-based medications has made it difficult for people to think clearly about the potential value of pharmacological therapeutics directed toward our natural endocannabinoid chemistry.

The idea of smoking marijuana to treat illness is already on its way to becoming a medical anachronism. Marijuana is passing into the same category as drinking foxglove tea to treat heart failure or chewing willow bark to treat pain and fever. The course of medicine has frequently begun with recognizing the value of folk remedies, extracting the essential active ingredients, and then modifying them to increase efficacy and safety. Foxglove became digitalis, and then digoxin. Willow bark led to synthetically produced salicylic acid – aspirin. Today's physicians eagerly await the next generation of cannabis-based medications to be developed by scientists even as the public is rushing headlong into widespread medicinal use of cannabis-based products, especially CBD.

As soon as the endocannabinoid system was discovered, with CB1 receptors primarily in the brain, CB2 receptors throughout the body and several natural neurotransmitters, attention turned to how altering the system's activity might treat disease. Raphael Mechoulam, the researcher introduced earlier as the "father of cannabinoid chemistry," led the way into exploring potential medical uses of cannabis. The possibility of developing cannabinoid-based medications makes sense given the ubiquity of our endocannabinoid system and the multiple functions it serves, from guiding development of the nervous system to regulating other neurotransmitters, our stress response, and the immune system. Mechoulam immediately recognized that targeting various portions of the endocannabinoid system to increase or decrease its activity could have immense practical value for alleviating suffering and treating disease. However, it is highly unlikely that the best way to take cannabinoid-based medications is to burn the raw plant and suck hot ashes into your lungs or take high doses of CBD or THC without medical supervision.

The Science

The National Academies of Sciences, Engineering, and Medicine recently published a comprehensive review of over 10,000 journal articles to assess the level of scientific evidence supporting medical benefits of marijuana.[3] This is not an exhaustive review of *potential* medical benefits, but rather a rigorous analysis of currently available research evidence that has been generated in a political climate often hostile to such research. U.S. researchers' hands have been tied by the Drug Enforcement Agency and the FDA's continued insistence on keeping marijuana a Schedule I drug declared to have a "high potential for abuse" and "no currently accepted medical treatment use." Neither assertion is true. Politics and morality frequently find scientific facts too inconvenient to accept. When reality is denied because its implications disturb a political/moral agenda, we are left in a fantasy world. More to the point, our leaders have damaged their integrity and truth-tellers become the enemy.

Nevertheless, the National Academies, with its scientific reputation on the line, reported the following:

- There is conclusive or substantial evidence that cannabis or cannabinoids are effective:
  - For the treatment of chronic pain in adults
  - As anti-emetics in the treatment of chemotherapy-induced nausea and vomiting
  - For improving patient-reported MS spasticity symptoms
- There is moderate evidence that cannabis or cannabinoids are effective for improving short-term sleep outcomes in individuals with sleep disturbance associated with

- Obstructive sleep apnea syndrome
- Fibromyalgia
- Chronic pain
- Multiple sclerosis

The list of health benefits documented by the National Academies is not overly impressive, although conclusive evidence of benefit for chronic pain sufferers, particularly in an era when the dangers of chronic use of opiate pain relievers has finally been recognized, is important enough by itself to be exciting. The report also evaluated the evidence for negative side effects, but was not designed to reconcile the potential harms and benefits of cannabis. What it did accomplish was to drive another stake in the ground supporting undeniable medical benefit for certain conditions. We can only hope that the National Academies' recommendation for further research will not continue to go unheeded by those who ignore and deny science out of fear, moral judgments, or political expediency.

Those who have followed the cutting edge research on cannabinoid chemistry are not surprised by the National Academies' report. Raphael Mechoulam has consistently predicted that therapeutic applications for cannabinoids will be found, asserting, "I believe that the cannabinoids represent a medicinal treasure trove which waits to be discovered."[4] These exciting treasures are currently being explored on the preclinical level of animal research in university, government, and pharmaceutical company labs around the world as they all race to bring new medicines into use.

The Internet provides opportunities for everyone to follow this research. For example, YouTube contains lectures[5,6] and interviews[7] by and about Dr. Mechoulam. PubMed also gives everyone access to all the medical literature published in English. Unfortunately, only the abstracts of scientific papers are generally available. Nevertheless, anyone can learn to type in whatever disease they wish to explore along with words like "marijuana," "cannabis," "THC," or "CBD" to receive a list of abstracts that may be of interest.

Bone Fractures and Osteoporosis

In a 12-minute video,[8] Mechoulam explains how his Israeli colleagues Yankel Gabet and Itai Bab teamed with researchers in Switzerland and Sweden to demonstrate quite convincingly that cannabinoid stimulation reduces the time for bone fractures to heal.[9] Scientists are now hoping to develop cannabinoid medications in the foreseeable future that increase bone density to prevent and treat osteoporosis, as well as to speed the healing of fractures.

Bones contain two cell lines with opposite functions. Osteo*blasts* lay down new bone while osteo*clasts* break bone down. Cannabinoid receptors are found on both. Proper balance between the two types of cells is necessary for bone health. Previous research had already shown that THC and CBD stimulate osteoblasts and inhibit osteoclasts. With apologies and gratitude to the mice in their experiment, Gabet and Bab studied the healing of a standardized femur fracture. They then measured bone healing in mice treated with THC, CBD, and both. The nonpsychoactive component of marijuana – CBD – most effectively promoted healing. CBD activated the bone producing osteoblasts and also increased crosslinking among collagen fibers where the osteoblasts lay down callous to bridge the fracture. The mid-femur fracture healed in 30% less time with CBD

administration. If there is any justice as far as the mice are concerned, veterinarians will likely be treating their animal cousins' fractures with cannabinoid medications before approval for human use.

Mechoulam began putting together research on CBD's beneficial impact on bone healing with what initially seem like random facts. He noted a study showing that Greek women have 50% less osteoporosis than women from northern European countries. The Mediterranean diet relies heavily on olive oil. Oleoyl, a constituent of olive oil, has a molecular structure almost identical to the natural cannabinoid anandamide. Oleoyl is present in bone as well, where it stimulates osteoblasts, the bone forming cells. Mechoulam began to ask if olive oil helps prevent osteoporosis, and by extension if cannabinoids could do the same. A mouse model for osteoporosis was developed and CBD was shown to reverse the process. There is, therefore, sound evidence that cannabinoid-based medications will, at some point in the future, probably make substantial contributions to women's bone health, reduce the hip fractures that so commonly result from osteoporosis, and reduce the time to heal all bone fractures by nearly a third.

Head Trauma and Stroke

Another promising area involves head trauma and stroke. The level of our natural endocannabinoid 2-AG in the brain rises rapidly following closed head trauma (again, in mice), reaching ten-fold normal levels after four hours. A single dose of 2-AG given within the first hour post-trauma reduced swelling and the volume of tissue death.[10] In addition, neurobehavioral status of the mice treated with 2-AG displayed greater recovery at 24 hours after injury. Return of function became even more pronounced by three weeks and was sustained throughout the length of the study. Studies of stroke, in which arteries to the brain are blocked for 30 minutes before blood flow is restored, show similar benefit from administration of CBD.[11] These results, in combination with other studies, contributed to Mechoulam's contention that the endocannabinoid system is uniquely positioned to perform a neuroprotective function in the face of brain injury and stroke. The data is clear, in mice. Similar results have been documented in 90-minute blockages of coronary arteries in rabbits.[12] Cannabinoid chemistry should be considered for the treatment of traumatic brain injury and ischemic events such as heart attacks and stroke. The FDA granted Revive Therapeutics, a company that specializes in cannabis-based pharmaceuticals, permission through an Orphan Drug designation to investigate CBD to prevent ischemia and reperfusion injury to solid organs being prepared for transplantation, which recently led to its introduction into the market.[13] It is entirely conceivable that paramedics one day will be authorized to administer a cannabinoid-based medication to stroke and heart attack victims as standard treatment on the way to the hospital.[14]

Pain

Cannabinoid preparations have long been used as folk medicine to relieve pain and now enough peer-reviewed studies have been conducted for the National Academies of Sciences, Engineering, and Medicine to conclude, "There is conclusive or substantial evidence that cannabis or cannabinoids are effective . . . For the treatment of chronic pain in adults." End of discussion – cannabinoid stimulation reduces some types of pain. The location of our endocannabinoid system in the spinal cord and pain circuitry in the brain

certainly supports this fact. *But*, are cannabinoid medications the clinically best, most effective choice with the fewest side effects? Therein lies the question.

Evidence for cannabinoid-based pain relief comes from animal as well as human studies. For example, recent research shows synergistic effects in rats of morphine and a CB2 stimulating medication. The combination reduced inflammatory, post-operative, and neuropathic pain more than morphine alone while preventing opiate-induced side effects such as constipation and addiction.[15] Furthermore, compounds that inhibit the breakdown of anandamide and 2-AG, thus prolonging their effect and increasing cannabinoid tone, also decrease the amount of opioids needed for pain control.[16]

Chronic inflammatory and neuropathic pain (arising from damage to nerves themselves) is decreased by endocannabinoids more than acute pain. The level of 2-AG rises in inflammation caused by tissue trauma, infection, or autoimmune reactions. This rise in 2-AG levels is now seen as modulating the inflammatory response and raising cannabinoid levels further by administering CBD has been shown to reduce inflammation, thereby reducing pain.[17]

The National Academies also based their conclusion on the natural experiments conducted in states that now permit use of marijuana for medically sanctioned purposes. Quoting from their 2017 report,[18] "Relief from chronic pain is by far the most common condition cited by patients for the medical use of cannabis. For example . . . 94 percent of Colorado medical marijuana ID cardholders indicated 'severe pain' as a medical condition.[19] Likewise . . . 87 percent of participants in [a separate] study were seeking medical marijuana for pain relief."[20]

While this data could be easily dismissed as merely documenting the most popular, and most difficult to disprove, excuse for obtaining a medical marijuana card, there is more to the story. The National Academies went on to cite evidence that some individuals are replacing the use of conventional pain medications (i.e., opiates) with cannabis. For example, one recent study reported survey data from patrons of a Michigan medical marijuana dispensary suggesting that medical cannabis use in pain patients was associated with a 64% reduction in opioid use.[21] Similarly, recent analyses of prescription data from Medicare part D (the prescription medication benefit) enrollees in states with medical access to cannabis suggest a significant reduction in the prescription of conventional pain medications.[22] Combined with the survey data suggesting that pain is one of the primary reasons for the use of medical cannabis, these recent reports suggest that a number of pain patients are replacing the use of opioids with cannabis, despite the fact that cannabis has not been approved by the FDA for chronic pain.

The impact of medical marijuana laws is put in stark relief by concurrent reductions in opiate overdose deaths. Approximately 60% of all opioid analgesic overdoses occur among patients who have legitimate prescriptions. Between 1999 and 2010, states with medical cannabis laws saw a mean of 24.8% fewer opioid overdose deaths compared with states without medical marijuana laws.[23] This is a strong indication of harm reduction that needs to be factored into public health policy along with whatever potential harms might be associated with medical marijuana laws.

Cancer

Cancer is still a scary word. Compassion for patients' suffering from cancer and its harsh treatments led to early acceptance of the symptomatic relief provided by marijuana for

pain, chemotherapy-induced nausea, and weight loss. Medical literature confirms marijuana's effectiveness with these three symptoms. At the same time, anecdotal reports of cancer cures by patients using marijuana have circulated. Since no number of anecdotes ever amounts to truly reliable data, and since legal restrictions surrounding Schedule I drugs have delayed the rigorous clinical research of these reports, little scientific progress has been made in establishing their validity. Nevertheless, laboratory and animal research has continued to accumulate regarding the antitumor impact of stimulating cannabinoid receptors in some varieties of cancer cells. The data is still preclinical, meaning that cannabinoids have shown an ability to inhibit growth and sometimes kill a variety of cancer cells in petri dishes, as well as to reduce growth and spread of cancer cells implanted in animals, but we do not yet know how robust these results will be in human cancer patients.

Of particular interest is an aggressive form of brain cancer called glioblastoma multiforme, which is highly resistant to current anticancer treatments. The prognosis is dismal, with life expectancy after diagnosis of approximately 12 to 15 months, even with surgery, radiation, and temozolomide, the current chemotherapy of choice. Researchers study new treatment options with human glioblastoma cells that have been transplanted into mice. THC alone inhibits the growth of transplanted glioblastoma tumor cells, as does a half dose of THC combined with the same amount of CBD. More importantly, combining THC or THC and CBD with temozolomide has a greater effect than either agent alone. The combination also was able to inhibit cancer cell lines that were resistant to either of the agents alone.[24] In the laboratory and animal studies, CBD has been shown to inhibit the progression not only of glioblastoma, but also breast, lung, prostate, and colon cancer.[25] CBD complements paclitaxel, used in breast cancer, by reducing the drug's toxic neuropathic effects.[26] In summary, preclinical data support the potential for cannabinoids to be direct inhibitors of some tumor progression as well as enhancers of first-line therapies, but should be viewed as still quite preliminary.

Multiple Sclerosis

Cannabinoid medication produces dramatic symptom relief in MS, a neurodegenerative disease in which the fatty layer (myelin) insulating nerve tracts is damaged. Progressive worsening of symptoms can be intermittent or unremitting and include double vision, muscle weakness, incoordination, anxiety, painful spasticity, and cognitive impairments. The name "multiple sclerosis" refers to the numerous scars, called plaques, that gradually accumulate in the white matter of the brain and spinal cord. The cause of MS is unknown and no cure currently exists. The average life span is 5–10 years lower than the general public.

A large number of MS suffers have found that marijuana provides significant relief from their painful spasticity and incoordination. I witnessed this in an octogenarian retired University of California Berkeley professor. She described being unable to walk in the morning until she quieted the tremor in her legs with whatever marijuana she was able to obtain. Initially skeptical, I found the following illustration of what she was experiencing published in 1997.[27] The left column is an MS patient's signature, spiral, and straight line drawings disrupted by his tremor. The right column is the same patient after being given 5 mg of THC. You do not have to be a rocket psychiatrist to see the difference (Figure 10.1).

I was able to prescribe pharmaceutical grade THC (Marinol) for my patient and she was able to get CBD oil from a compounding pharmacy, but we never gained access to the

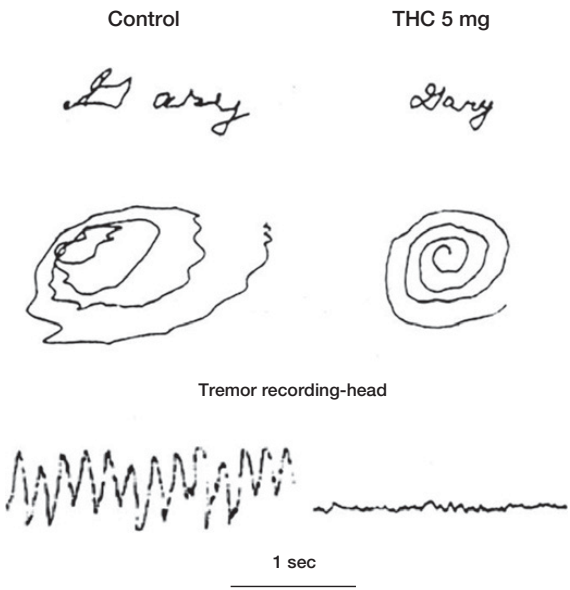

Figure 10.1 Multiple sclerosis patient after 5 mg THC. Source: R. G. Pertwee, 1997, "The therapeutic potential of cannabis and cannabinoids for multiple sclerosis and spinal injury," *Journal of the International Hemp Association* 4(1): 1, 4–8. ©American Neurological Association.

one medication (Sativex) available in England and Canada to treat MS. Sativex (GW Pharmaceuticals, Cambridge, UK) is a cannabis plant extract nasal spray containing a balanced mixture of THC (27 mg/ml) and CBD (25 mg/ml). Sativex still remains unavailable in the U.S.

There may be, however, a very real fly in the ointment for MS patients using marijuana. Multiple studies show that cannabis-using MS patients suffer greater cognitive decline than non-using MS patients, though some of the marijuana users may have started early in their teens.[28,29] MRI scans reveal cannabis use in MS results in greater loss of brain volume than non-users, which correlate with more cognitive deficits.[30] One other study found no increased cognitive decline in MS patients naïve to cannabis before being given Sativex (balanced THC and CBD) for up to six months.[31] Cognitive testing did not seem as rigorous in this study and exposure to cannabinoids was shorter, but the modulating effect of CBD on THC suggest directions for further research.

These results regarding the effect of cannabinoids on cognition in MS are a perfect example of where science often leaves us – between a rock of some facts and a hard place of other equally valid facts. The only way through such gray areas is an artful mixture of acknowledging the known benefits and risks mixed with an empathic caring for the human being in front of us. What does each unique individual value more – being able to walk now versus possibly fading mentally later? Each individual has her or his own view of wisdom and physicians need to help patients come to their own understanding of what course of action is in their own best interests.

Gastrointestinal Disease

Some of the oldest historical mentions of the medical use of cannabis involve gastrointestinal (GI) illnesses. This was dramatically brought to my attention by a patient

whose variety of physical complaints had been treated by a physician who aggressively promoted the use of marijuana. She had gladly cooperated with his recommendations since she had already used marijuana on a daily basis for over 40 years. When she began seeing me for advice regarding her relationship with a grown daughter, the woman was smoking an impressive amount of marijuana each day, beginning with a bowl before getting out of bed every morning. After getting to know me enough to reveal more personal information, she began revealing her strange bowel habits. For a few years now she had not had a spontaneous bowel movement but had relied on daily coffee enemas. As you might imagine, she had grown weary of this practice.

I knew that cannabis was used for millennia to treat diarrhea so I reviewed the scientific literature. The endocannabinoid system has been found throughout the gut. Mechoulam had first isolated 2-AG from dog intestines. Nerves containing CB1/CB2 receptors, anandamide, and 2-AG regulate the stomach, small, and large intestine. Variations in cannabinoid tone impact a dizzying array of functions in the gut, from motility to food intake, nausea and vomiting, gastric secretion, visceral sensations, and intestinal inflammation. Increasing cannabinoid tone by administering THC or by blocking fatty acid amide hydrolase (FAAH), the enzyme that breaks down anandamide, slows down intestinal peristalsis (the rhythmic squeezing that moves intestinal contents along). Decreasing cannabinoid tone by administering the cannabinoid blocker SR141716 (rimonabant) increases motility. In fact, one of the side effects of using SR141716 for weight loss is diarrhea.[32,33] I diagnosed the woman as having a marijuana-induced "atonic colon," meaning that it was no longer able to squeeze hard enough to move her bowels. It is possible that SR141716 would have reversed the process (if it were even available), but the potential for precipitating sudden and complete cannabinoid withdrawal would have been a very discomforting possibility. The only remedy was abstinence. She entered a treatment center for three months where she could be monitored by a gastroenterologist. It took nearly the full three months for remission of her symptoms and re-establishment of normal intestinal motility.

Because the endocannabinoid system is such an intimate part of the GI system, the possibility exists for developing cannabinoid-based medications as new treatments for a variety of conditions, including chronic constipation, diarrhea, gastric-esophageal reflux, irritable bowel syndrome, and inflammatory bowel disease (Crohn's disease) to name a few. Currently, the side effects associated with marijuana (i.e., dizziness, dry mouth, fatigue, euphoria, drowsiness) have limited its use in treating GI disease. However, given our ability to discover new, or modify current cannabinoid stimulating and blocking molecules, and to develop medications that alter the levels of anandamide and 2-AG, it seems a matter of time before cannabinoid-based medications are in common use to treat GI disease. At a minimum, it should be possible to attach THC, CBD, or SR141716 to other molecules that will permit them to impact cannabinoid receptors in the gut to treat diarrhea and constipation respectively without being absorbed into the blood stream and causing unwanted side effects.[34] In an analogous way, naloxegol (Movantik) treats opioid induced constipation by attaching an opiate blocker to a molecule that prevents its crossing the blood-brain barrier, thereby causing withdrawal in the gut without precipitating generalized withdrawal.

Stress Response

It is also likely that cannabinoid-based medications will soon protect us in a more general way from the damage done by excessive stress. Everyone wants to reduce the physical and emotional impacts of excessive stress and the endocannabinoid system clearly plays a role in modulating our body's stress response. A complex and fascinating cascade of events is set in motion by a wide variety of physical and psychological disturbances, from injury and disease to cold, fatigue, alcohol, and fear, to name but a few. The major hormonal response to any strain, emotional or physical, occurs in what is called the hypothalamic–pituitary–adrenal (HPA) axis. The hypothalamus lies at the base of the brain and receives sensory, emotional, cognitive, and memory input from other parts of the brain. Whenever inputs to the hypothalamus signal a threat, it drips a releasing factor into the pituitary gland hanging just below. The pituitary then secretes a hormone (ACT) into the bloodstream to signal the adrenal glands on top of the kidneys to pump the stress hormone cortisol into the blood. Cortisol contributes to the "fight-or-flight" response by mobilizing glucose from the liver to power the heart and muscles to run fast or fight fiercely. All energy is diverted toward dealing with the threat at hand and away from normal functions such as growth, reproduction, the immune system, and digestion. In the short run and in the face of real threats, cortisol, in combination with a surge of adrenaline, is very adaptive. But encounters with lions are rare today and the HPA axis continues to respond for many of us as though homework deadlines, social rejections, and late car payments are a matter of life and death. As a result, chronic stress, with its elevation of cortisol, can be quite deleterious when it lowers immune function and bone density, increases weight, blood pressure, cholesterol, and heart disease, to name the top of the list of negative impacts.

The HPA axis and areas of the brain connected to it (especially the amygdala, hippocampus, and frontal cortex) are all modulated by the endocannabinoid system. CB1 receptors, anandamide, and 2-AG are all present throughout the entire HPA. Initial research on the effects of marijuana on our stress response mechanisms found that THC increases HPA activity[35,36] and cortisol levels (an effect that fades with repetition), while CBD reduces HPA activity.[37] However, administering THC or CBD does not give an accurate picture of the basic role endocannabinoids play in the ongoing regulation of our HPA axis and the stress response. It has now been shown that our endogenous cannabinoid system inhibits HPA axis activity, thereby maintaining lower basal levels of cortisol. And the endocannabinoid system restricts HPA axis activity in situations of acute stress.[38] Mice that are genetically altered to have no CB1 receptors have high HPA activity and cortisol levels[39] and blocking CB1 receptors with SR141716 in normal rats increases cortisol.[40]

The HPA axis undergoes important development during adolescence, beginning with its activation of sexual hormones in puberty, and stress responses are distinctly different from that of the mature adult HPA axis. Research needs to rely on animal studies here for ethical reasons. Chronic THC during adolescence results in long-term neural and behavioral changes in rodents similar to those produced by chronic stress.[41] Once again we see the pattern of adolescents being at higher risk from marijuana use due to ongoing neurodevelopment during this critical period of life.

Interactions between the endocannabinoid system and the HPA axis are complex enough that research is still needed to sort out the fine details. Nevertheless, we do

now know that the presence of endocannabinoids within the hypothalamus, as well as in upstream structures such as the amygdala, suggests an important role in regulating our response to stress. The existence of this relationship provides an opportunity for medical intervention by developing cannabinoid-based medications to treat diseases exacerbated by excessive activation of our stress response mechanisms, (e.g., heart disease, hypertension, obesity, sleep disorders, post-traumatic stress disorder, etc.).

Post-Traumatic Stress Disorder

Post-traumatic stress disorder (PTSD) has received a great deal of attention as a potential target for treatment with cannabinoid medications. There is a myriad of anecdotal reports of marijuana's significant reduction of PTSD symptoms, such as hyperarousal, emotional distress, flashbacks, and intrusive thoughts of the trauma. This is especially true in the popular press and on the Internet regarding military combat veterans. The concept of marijuana use as a form of self-medication for PTSD has become accepted as conventional wisdom by much of the general public.

Fear in the face of serious threats activates our physical defenses, but over time we normally find ourselves able to remember the threatening moments with less activation. In PTSD, the process of aversive memories fading with time is damaged. Four groups of symptoms found in PTSD are (1) reliving the trauma (nightmares and flashbacks), (2) avoiding reminders of the trauma (refusing to talk about the trauma and isolating), (3) mood disturbances (survivor guilt, shame, and depression) and (4) hyperarousal (irritability, startle reactions, insomnia, and difficulty concentrating). These symptoms are often quite resistant to psychological and pharmacological treatment.

An interesting report emerged in 2009 from one of the Trauma and Stress Support Centres run by the Canadian Armed Forces Mental Health Services. A group of patients with PTSD who continued to have nightmares after conventional pharmacological treatment (SSRI antidepressant and/or benzodiazepines such as diazepam) were given a synthetic cannabinoid called nabilone that mimics THC. The trial was marred by the lack of a placebo control to measure the psychological impact of having hopes raised by a new medication. Nevertheless, a remarkable 72% experienced either cessation of nightmares or a significant reduction in nightmare intensity.[42] A similar report in 2014 from New Mexico, also marred by the lack of a control group, indicated a 75% reduction in PTSD symptoms with medical marijuana.[43] These results recall the important work of Marsicano (Chapter 2), who discovered that the endogenous cannabinoid system has a central function in the extinction of aversive memories. Marsicano showed that forgetting is an active process under endocannabinoid control. Blocking cannabinoid tone with SR141716 blocks extinction of fear responses, while increasing cannabinoid tone hastens extinction of fear responses.[44] PTSD can therefore be seen as a failure of endocannabinoid-based extinction of the fear associated with any reminder (external or internal) of the original trauma. The Canadian study used nabilone and the New Mexico study used marijuana to increase cannabinoid tone and reduce intrusive nightmares.

What is true of mice is sometimes true of men. In 2012, Christine Rabinak and a team of researchers replicated Marsicano's animal studies with humans for the first time.[45] Their work showed that THC facilitates extinction of conditioned fear in humans. After establishing a conditioned fear reaction, measured by galvanic skin response, one group

in this methodologically sound study received placebo two hours before an extinction protocol while the other group received THC. Those who received placebo exhibited return of fear to the conditioned stimulus 24 hours later, whereas THC recipients had a reduction in recurrence of fear. One year later a London-based group confirmed these results by giving CBD at different times during the conditioning and extinction process.[46] They found that the most effective time to administer CBD was *after* extinction of the fear response. This timing greatly reduced the incidence of reactivation of the fear response. Too often exposure therapies capable of quelling PTSD symptoms have provided only temporary relief. These results suggest exploring whether a course of CBD following exposure therapy or eye movement desensitization and reprocessing (EMDR) treatment could better consolidate the benefit.

An alternative exists to administering cannabinoid stimulants (i.e., nabilone, THC, anandamide, or 2-AG) for enhancing extinction of fear. Endocannabinoid activity is regulated by an enzyme – FAAH – that breaks down anandamide. When FAAH is blocked (for example, by AM404 or URB597), the activity of anandamide is increased. We always need to remember that anandamide and THC are not the same. THC has a stronger and longer impact on cannabinoid receptors.[47] Nevertheless, reducing FAAH and thereby indirectly increasing anandamide also enhances extinction of fear responses.[48,49]

The level of FAAH available to break down anandamide is also impacted by our genetic makeup. DNA variations in genes for FAAH exist, leading to different forms of the enzyme that are associated with different levels of threat-related activity in the amygdala in different individuals.[50] Approximately 38% of European ethnic stock carry a variant of FAAH with reduced activity that selectively enhances extinction of fear-based learning.[51] It remains to be determined whether this genetic variant is associated with a reduced risk of PTSD.

Returning to the question of marijuana as treatment for PTSD, I think the science points to something real happening here. But the more science teaches us, the more complex issues become. The challenge is to use current scientific understanding to develop better questions. It is now clear that our endocannabinoid system is intimately involved with fear reactions, physiological responses to fear, and the effective passage of threatening events from continuously remaining in the present into memories able to contain our fear. The critical question facing us is whether smoking marijuana is the best way to heal PTSD. Is THC the best medicine, or CBD, or an FAAH inhibitor, or something else? Is adding marijuana's cannabinoid stimulation better than finding ways to increase the body's natural cannabinoids? One important approach to answering these questions is to look at the side effect profile of the different potential medicines. CBD is less psychoactive than THC. Chronic use of THC downregulates CB1 receptors, with all the impacts outlined in Chapters 5–7, while CBD does not cause downregulation. I am also reminded of Staci Gruber's masked faces research (Chapter 6) showing that the amygdala in marijuana users processes emotional stimuli differently. How much distance from present emotional realities can be tolerated with PTSD medications? THC also carries the risk of addiction. According to the National Epidemiologic Survey, nearly a third of individuals using marijuana experience clinically significant impairment or distress related to marijuana use.[52] The National Center for PTSD states that there were more than 40,000 veterans seen in the U.S. Department of Veterans' Affairs with both PTSD and CUD in 2014.[53] How does the irritability of THC withdrawal interact with the hyperarousal of PTSD for those relying too heavily on marijuana to subdue their symptoms? My best guess is that different treatments will be found to work better for

individuals with different genetic configurations, and medications that increase natural endocannabinoid tone will eventually be found to have fewer side effects than the external stimulation offered by marijuana. Even when more targeted treatments become available, we can expect that the daily high provided by marijuana will remain seductive for many.

Neurodegenerative Disorders: Alzheimer's, Parkinson's, Huntington's Chorea, Amyotrophic Lateral Sclerosis, and Retinal Degeneration

As if it were too much to ask, the endocannabinoid system has been shown not only to regulate neuronal homeostasis but also to promote neuronal survival. Neuroprotective properties stem from a combination of effects that preserve, rescue, repair, and replace diseased and damaged neurons.[54,55] While evidence for potential novel ways to treat acute and chronic neurodegenerative disorders is promising, research is currently largely preclinical (i.e., animal studies) and animal models of specific neurodegenerative diseases only approximate human disorders. We need to bear in mind when reviewing positive preclinical results that human clinical trials conducted so far have failed to demonstrate beneficial effects. On the other hand, human trials have generally focused on alleviating specific symptoms rather than studying the impact on underlying disease processes or controlling disease progression. And more sophisticated experimental designs that elevate endogenous cannabinoids by inhibiting enzymatic breakdown of anandamide and 2-AG still need to be undertaken. Nevertheless, enough strong evidence exists to warrant a brief review in order to prepare readers to understand anticipated future developments in this area.

One specific example illustrates the character and quality of evidence supporting the endocannabinoid system's neuroprotective properties. The HIV-1 virus does not infect neurons, but does its damage by producing viral toxins that disrupt neuronal calcium equilibrium and give rise to synaptodendritic injuries and cell death. The excitotoxicity these toxins produce in a culture of prefrontal cortical neurons is accompanied by upregulation of CB1 receptors. The direct application of anandamide and 2-AG reduces toxin-induced excitotoxicity and increases neuronal survival. The CB1 antagonist SR141716 blocks the neuroprotective effect of anandamide and 2-AG, which proves their impact is receptor mediated.[56]

The endocannabinoid system's neuroprotection goes beyond CB1 and CB2 receptor activation. The Madrid researcher Javier Fernandez-Ruiz argues that the endocannabinoid system has broad-based ability "to limit the influence of multiple cytotoxic stimuli (e.g., excitotoxicity, oxidative stress, inflammation, etc.) on neuronal homeostasis and survival."[57] This wide spectrum of effects, from reducing toxic levels of neuronal excitability by normalizing glutamate homeostasis to reducing oxidative injury and attenuating local inflammatory events, offers extraordinary potential for developing new medications for several neurodegenerative disorders. Because neurons in these disorders suffer from a combination of damaging forces, a combination of protective effects is needed – the combination uniquely provided by the endocannabinoid system's action on both neurons and their supporting glial cells throughout different areas of the brain.

Cannabidiol

Unfortunately, many (if not most) studies of the medical benefits of marijuana have not reported the ratio of THC and cannabidiol (CBD). The cannabis plant contains complex

and variable chemistry and different varieties produce marijuana with widely different mixtures and concentrations of multiple cannabinoids and terpenes that complicate research on the medical uses of marijuana and diminish the reliability of its results. Because of its strong psychoactivity THC alone is easier to study in animals, where negative side effects are less troublesome than in humans. CBD alone is far better tolerated and thus easier to use in human studies. As a result, it is now becoming apparent that many benefits attributed to marijuana are produced primarily by its CBD, although the impact of THC itself as well as interactions between THC and CBD cannot be ignored. Nevertheless, separating out the medical benefits of CBD alone helps clarify the overall picture of medical marijuana.

Background

Because of its current popularity and the sheer volume of questions people have about CBD, the topic needs to be given specific attention. However, any summary of the impacts of CBD on the brain quickly becomes unfathomably complex. The bottom line is that we do not know enough to say simply and definitively what CBD does in the body, in part because it is involved in a dizzying array of physiologic processes, many of which are still only partially understood. At the same time, evidence of its medical benefits and safety is growing increasingly strong. Large segments of the public are gravitating toward its use, both for good reasons and in response to overpromising anecdotes circulating on the Internet and promoted by industry marketing. (Apropos of such marketing, I just received a free premier issue of the new natural health magazine *CBD Snapshot*.) It therefore behooves clinicians to be aware of what we know about CBD, how we know it, and how much is not yet known.

Cannabidiol was first isolated from Minnesota wild hemp in 1940.[58] It was not until 1963 that the exact structure was discovered and synthesis achieved by Raphael Mechoulam one year before he purified THC and established its structure.[59] Much less research was initially done on CBD than THC because of its relative lack of psychoactive properties compared to THC's dominant role in producing marijuana's psychoactive powers. When it was recognized that different samples of marijuana produce varying results for different research laboratories despite containing equal amounts of THC, attention turned to the other cannabinoid chemicals, especially CBD, as potential modifiers of THC's effects. The complexities of CBD were quickly encountered when researchers began exploring its interaction with THC. Administering CBD before THC increases THC's effects, while administering both together decreases THC's effects. The explanation for these seemingly contradictory actions is that CBD inhibits metabolism of THC by the liver, so pretreatment causes higher levels to reach the brain. Simultaneous dosing with CBD and THC does not provide enough time for this inhibition of metabolism to affect THC levels, and in this case CBD's antagonism of THC (eventually shown to occur at the CB1 receptor level) lowers THC's effects.[60] This antagonism of THC by the simultaneous administration of CBD explains why different strains of marijuana with the same level of THC but different levels of CBD have different effects.

The CBD preparations marketed today come from three sources. The strains of cannabis that give us marijuana (*sativa* and *indica*) contain THC and CBD as its two most abundant cannabinoid molecules. Both THC and CBD come from the same

nonpsychoactive precursor cannabigerol (CBG). Because the amount of CBG is limited, the amounts of THC and CBD produced by any given strain are inversely related. High THC means low CBD, and vice versa. These two end products reflect the relative abundance of synthetic pathways for each in any given strain. Horticulturists have bred strains with increasing proportions of THC (i.e., skunk) and CBD (i.e., Charlotte's Web).

CBD is also harvested from industrial hemp plants that contain virtually no psychoactive cannabinoids. Hemp oil, produced from hemp seeds for cooking and industrial uses, contains only trace amounts of CBD (25 parts per million). CBD oil is produced from hemp stalks, leaves, and flowers and contains up to 15% CBD. Finally, CBD can also be produced synthetically.

CBD's mechanism of action in the brain occurs in multiple ways. To begin, its direct stimulation of typical endocannabinoid CB1 and CB2 receptors is almost negligible. Because CBD competes for CB1 receptors and is much less activating than THC, anandamide, and 2-AG, it partially antagonizes them, reducing their impact.[61] This antagonism of THC helps explain CBD's role in protecting against some of THC's negative effects. On the other hand, CBD does interact directly with a subset of serotonin receptors ($5\text{-}HT_{1A}$) that reduce anxiety and autonomic stress responses.[62] CBD also interacts with other lesser known receptors such as TRPV1, which contribute to heat, inflammatory, and pain sensations – all functions having medicinal import.[63]

A more interesting, and complex, mechanism for CBD's interactions with the brain involves the phenomenon of "functional selectivity." Understanding functional selectivity begins with recognizing that it is a gross oversimplification to view the impact of a neurotransmitter's arrival at its receptor as having an either/or effect – either stimulating or suppressing postsynaptic neuronal activity. Neurotransmitters, including the endocannabinoids anandamide and 2-AG, give rise to a multitude of events, called signal transduction pathways, when they activate receptors. The concept of functional selectivity helps explain why different cannabinoid molecules have different effects at the same receptor. When THC enters a CB1 receptor, it does not activate the same set of signal transduction pathways as anandamide or 2-AG. This different impact, in combination with THC's greater affinity (i.e., strength of *connectedness* to receptors), explains the different effects of THC. Most importantly for our purposes, *adding CBD to the mix alters the signal transduction pathways activated by anandamide, 2-AG, and THC.*[64] CBD alters how cannabinoid receptors respond to anandamide, 2-AG, and THC, modifying the impact of each and thereby reducing some of the unwanted side effects of THC.

An analogy to broth, soup, and stew is useful here. If the either/or view of neurotransmitter-receptor interaction is mere broth, the multiple different pathways activated in postsynaptic neurons produces a more complex soup of effects. Then, when functional selectivity permits different molecules to activate different pathways by interacting in unique ways with the same receptor, we begin seeing a complex stew of even more varied ingredients. Finally, CBD can be seen as the spice added to this stew, further modifying the functional impact of all endogenous and exogenous molecules that interact with receptors – a gourmet's delight of infinitely nuanced flavors and nearly incomprehensible complexity.

The vast majority of people seen by clinicians, and perhaps most clinicians themselves, have little interest in the above details. I provided a superficial outline of the mechanisms for CBD's interactions with the brain in order for clinicians to say with

authority and integrity, "It's complicated, and still needs more research to be fully understood." All the public wants to know is, "Is it safe and does it work?"

While the question of safety can never be answered with a definitive guarantee (science can never prove a null hypothesis), reliable reviews of the medical literature are quite reassuring regarding CBD's safety and side effects.[65,66] Very importantly, the World Health Organization has concluded *CBD exhibits no effects indicative of any abuse or dependence potential*,[67] an opinion confirmed by Alan Budney, who delineated the criteria for THC dependence and withdrawal.[68] No reports of recreational use or abuse of pure CBD have emerged from the streets.[69] The most common side effects are tiredness, diarrhea, and changes of appetite/weight. CBD has a better side effect profile than many drugs used to treat conditions for which CBD is also used. When used as adjunct therapy, CBD often successfully reduces the dose of standard medications, including anticonvulsants and opiates. Nevertheless, the impact of long-term CBD use and its interactions with most other drugs have not yet been fully investigated and cannot be accurately predicted, especially for neurodevelopment in children and adolescents.

A review of medical literature on the potential therapeutic uses of CBD by Esther Blessing in 2015 concluded: "Preclinical and clinical studies show CBD possesses a wide range of therapeutic properties, including antipsychotic, analgesic, neuroprotective, anticonvulsant, antiemetic, antioxidant, anti-inflammatory, antiarthritic, and antineoplastic properties ..." in addition to significant antianxiety effects.[70] An anonymous online survey of CBD users found the top three medical uses are for pain, anxiety, and depression. The odds of using CBD to treat a medical condition were 1.44 times greater among nonregular users of cannabis than among regular users.[71] In my clinical practice, the three most common reasons people have asked about using CBD have been related to anxiety, insomnia, and chronic pain. Unfortunately, no formal FDA process has studied CBD's proper use, effectiveness, and side effects for these three conditions.

Anxiety

CBD's ability to reduce anxiety was first demonstrated in 1974 when it was shown to reduce anxiety associated with THC.[72] Later studies using appropriate rating scales confirmed this observation,[73] although CBD has little reduction of baseline anxiety in healthy individuals. Animal studies confirmed CBD's reduction of anxiety stimulated by protocols such as the elevated rat maze.[74,75] A double-blind study then showed CBD reduces anxiety stimulated in humans by situations such as speech presentations tests,[76] with an inverted U-shaped dose-response curve demonstrating loss of effectiveness at higher doses.[77] CBD's ability to reduce the response to anxiety-provoking stimuli is visually demonstrated by fMRI images in a double-blind, randomized, placebo-controlled study of people viewing faces designed to elicit different levels of anxiety. Pretreatment with CBD attenuates responses in the amygdala and attendant anxiety. The suppression of the amygdala response correlated with reduced fluctuations of skin conductance.[78] These results bring to mind Staci Gruber's masked faces protocol, which shows heavy marijuana users' reduced amygdala activation in response to fearful faces,[79] reviewed in Chapter 7, all of this being the "chill" many seek from marijuana.

In essence, CBD reduces "excess" anxiety, which makes it a good candidate to give relief to up to 33% of people with a lifetime history of an anxiety disorder.[80] Excessive fear

and anxiety are dominant symptoms in generalized anxiety, panic, post-traumatic stress, social anxiety, and obsessive-compulsive disorders. SSRIs, anticonvulsants (mood stabilizers), and benzodiazepines are the most frequently used medications to treat these often disabling conditions. Because of undesirable side effects from SSRIs, the addictive potential of benzodiazepines, and the limited effectiveness of all three, the potential of novel therapeutic approaches using cannabidiol are attracting attention.

Psychotic Episodes and Schizophrenia

As described in Chapter 7, CBD has a moderating effect on THC that reduces both the anxiety and potential for psychotic reactions THC causes. As a result, strains of marijuana called skunk that have very high THC:CBD ratios produce the highest rate of psychosis.[81,82] The suggestion that CBD could be beneficial in the treatment of schizophrenia has recently received serious attention. In a double-blind study, patients with schizophrenia randomly received either 1000 mg CBD or placebo daily alongside their existing antipsychotic medication. After six weeks, patients receiving CBD showed greater improvement in overall functioning (as measured by the Global Assessment of Functioning scale). CBD produced lower levels of positive psychotic symptoms and patients were more likely to have been rated as improved by the treating clinician.[83] Few adequate studies of CBD monotherapy for schizophrenia have been published. While a brief report of its use in three cases of treatment-resistant schizophrenia showed little or no benefit,[84] a well-controlled double-blind study in acute paranoid schizophrenics by Leweke did show equivalent efficacy for CBD versus an antipsychotic medication, with a better side effect profile.[85]

Leweke's 2012 paper suggests that, while THC exacerbates symptoms in schizophrenics and high doses cause psychotic symptoms in healthy subjects, the conclusion that hyperactivity in the endocannabinoid system causes psychosis may not be accurate. The rationale is interesting. First, the endocannabinoid antagonist SR141716, which reduces endocannabinoid activity, has no efficacy in treating schizophrenia.[86] Second, cerebrospinal anandamide levels are inversely correlated with psychotic symptoms in antipsychotic-naïve schizophrenic patients, i.e., higher levels of anandamide correlate with fewer symptoms.[87] And third, because CBD inhibits FAAH, the enzyme that breaks down anandamide, and thus enhances intrinsic anandamide signaling, Leweke concluded that CBD's ability to enhance anandamide levels might help explain its antipsychotic properties. Obviously, a lot still has to be sorted out here.

Finally, the working hypothesis regarding the genesis of schizophrenia has been dopamine dysregulation and overactivity in the mesolimbic system. All traditional antipsychotic medications have worked by blocking dopamine hyperactivity. THC and CBD have been found to have opposing effects on mesolimbic dopamine activity, with pro-psychotic THC increasing dopamine activity and antipsychotic CBD modulating dopamine hyperactivity both directly and by reducing downstream impacts on the prefrontal cortex.[88] Data and hypotheses regarding the endocannabinoid system's role in, and the potential for CBD treatment of, schizophrenia is complex and confusing currently. This is the nature of science as its most extreme cutting edge enters new territory. The value of wrestling with these uncertainties is to understand that anecdotes and claims about marijuana's beneficial impact on schizophrenia are unearthing something real, no matter how wild, unrealistic, and premature some claims may be.

Sleep

Early indications of CBD's sedative effect largely came from a Brazilian research team trained by the country's first psychopharmacologist, Yale educated Elisado Carlini. In the early 1970s, CBD was shown to decrease moving about by rats[89] and higher doses interfere with operant conditioning.[90] In 1977, CBD definitively demonstrated its sleep-inducing effects by increasing total sleep time in rats.[91]

Many studies of marijuana's impact on sleep in humans have been inconclusive, which may be the result of variable THC:CBD ratios in the varieties of marijuana used. THC clearly promotes sleep onset, but tolerance develops with chronic use and circadian rhythms are blunted.[92] CBD by itself has become popular for inducing sleep, though several of my patients have reported relatively rapid tolerance to its beneficial effects. Raphael Mechoulam reports CBD has a biphasic effect on sleep.[93] Low dose CBD (15 mg) reduces sleep and counteracts the sedative effect of 15 mg of THC. On the other hand, a larger dose of CBD (160 mg) causes significantly more sleep and less dream recall than placebo.[94] Because of lack of certainty about dose in CBD purchased both over the Internet and in dispensaries, it is difficult to know what to make of patients' stories of ongoing successful CBD use as a sleep aid. Given CBD's extremely safe side effect profile, I do not question patients' experience using it for sleep, though I would like more accurate information regarding their dosage.

Pain

As noted at the beginning of this chapter, the National Academies of Sciences, Engineering, and Medicine report determined there is conclusive or substantial evidence that cannabis or cannabinoids are effective for the treatment of chronic pain in adults. Millions of people worldwide already knew this. The Academies' contribution is to assert that scientific research now confirms this analgesic property as objective fact. What most people do not know is that the pain relief provided by typical NSAIDS (acetaminophen, ibuprofen, etc.) is due in part to enhancement of our endocannabinoid system by these drugs. Also known as COX-2 inhibitors, NSAIDS block the ability of an inflammatory enzyme to increase the breakdown of our natural cannabinoids.[95,96] The precise degree to which this augmentation of endocannabinoid activity contributes to the anti-inflammatory and analgesic effects of NSAIDS is unclear, but there is no doubt that both THC and CBD (and perhaps especially the two in combination) provide relief from chronic pain. Oral and transdermal CBD show substantial anti-inflammatory and analgesic properties.[97] Although reports of reduction in opioid dose and cessation of opioids by chronic pain patients using marijuana appear in the medical literature,[98] a four-year Australian study published in *The Lancet* found no such reduction in opioid use.[99] Instead, they found that the 60% of people choosing to use marijuana products had higher levels of generalized anxiety and lower pain self-efficacy scores. The relative role of THC and CBD in relieving chronic pain may receive some clarification by the FDA, which finally opened hearings on CBD (May 31, 2019). Unfortunately for those interested in trying CBD alone, dosage labeling of CBD products is disturbingly unreliable. A 2017 study found 7 of 10 CBD products did not contain the amount of extract promised. Nearly 43% contained too little CBD, while 26% contained too much.[100,101] In the "Wild West" of this largely unregulated new industry, *caveat emptor* – buyer beware.

Epilepsy

In 1973, the Brazilian research group led by Carlini reported the first experimental evidence that CBD reduces or blocks convulsions produced in rats.[102] A year later another Brazilian confirmed both CBD and THC, in that order of potency, decrease seizures stimulated in the hippocampus of rats.[103] Carlini's group then tested CBD as a treatment for intractable epilepsy in 16 grand-mal patients. Daily CBD (200–300 mg) or placebo was given to each in a double-blind procedure in addition to the usual anticonvulsant medications (which had not eliminated their seizures). Only one patient receiving CBD showed no improvement, while only one receiving placebo improved.[104]

As of today, only limited progress has been made in the clinical use of CBD to treat epilepsy despite one third of all epilepsy not being adequately controlled by available medications. In 2018, the FDA approved the first CBD preparation, Epidiolex (>99% CBD and <0.10% THC, from GW pharmaceuticals, Cambridge, UK), for treatment of two rare forms of severe pediatric epilepsy – Lennox-Gastaut (LGS) and Dravet syndromes – generally treated by specialists. LGS strikes children between three and five years old, causes frequent and multiple forms of seizures and lasts into adulthood 80–90% of the time. Dravet syndrome is a "catastrophic, lifelong form of epilepsy that begins in the first year of life with frequent and/or prolonged seizures"[105] often beginning with fevers and causing developmental delays. Both forms of childhood epilepsy place a heavy caretaking burden on families. The vast majority of random controlled and open-label studies confirm that adding CBD to current anticonvulsant medications results in significantly reduced frequency of seizures and increased quality of life for these rare forms of pediatric epilepsy, but insufficient studies have been conducted to determine CBD's effectiveness on other forms of epilepsy.[106,107]

The advent of Epidiolex removed one of the primary obstacles to rigorous research – the lack of purified CBD with its known dosage. In 2018, the University of Alabama at Birmingham reported an open-label study of CBD in 72 children and 60 adults with treatment-resistant epilepsy, starting at 5 mg/kg/day and titrating up to a maximum of 50 mg/kg/day (most between 20 and 30 mg/kg/day) added to their standard anticonvulsant medications. Both pediatric and adult patients experienced significant improvements in seizure severity, seizure frequency, and negative side effects by 12 weeks, with response maintained through 48 weeks of treatment.[108] These results warrant confirmation and refinement by randomized double-blind studies, and perhaps then by extension to patients who are well controlled by standard anticonvulsant medications to explore whether current doses and negative side effects can be reduced.

The FDA gave the green light to a second CBD preparation in 2018 for use specifically with organs being transported for transplantation. CBD reduces ischemic and reperfusion damage, thereby decreasing the rate of organ rejection. These benefits to transplant organs appear to mirror the protection against ischemic damage CBD provides in animal experiments that temporarily block blood flow to brain and heart.

More research is needed and should be generously funded. Tacking a call for more research onto a review of potential cannabinoid-based medications has become a threadbare cover for lack of resolve, in the face of political intransigence opposing anything related to marijuana, to follow the evidence wherever it leads. In the present

case, I hope it is seen as a genuine recognition of the important value such research will bring to the treatment of human disease and suffering.

Concluding Observations

The fate of my patient with no capacity to have a bowel movement introduces the topic of physicians' practices primarily focused on medical marijuana. Over half the U.S. population has legal access to marijuana for medical purposes. States differ in how long they have permitted medical use of marijuana, with California being the longest at nearly a quarter of a century. States also differ in the diagnoses for which physicians may recommend marijuana. As of March 2016, 1,246,000 Americans held medical marijuana cards, although there is no assurance all were currently using marijuana, nor that all medical marijuana patients had applied for official cards. And there is no way to estimate the percentage of card holders who are merely seeking legal protection for their recreational use, though this is generally acknowledged to be quite high. California has the largest number of card holders (759,000),[109] although Colorado has a slightly higher per capita rate (19.8 per 1000).[110] Depending on each state's laws, individuals may or may not require an official medical marijuana card to purchase marijuana at a dispensary once securing a physician's letter of recommendation, though carrying a card in order to have evidence of the legal right to possess marijuana may prove convenient. At this point these cards provide the only publicly available data regarding the number of medical marijuana users, but the figure is always an unreliable estimate of the actual number of users. In the case of my own home county, only two physicians known as "pot docs" write over half of the recommendations used to obtain cards, which is a common occurrence in many other areas.

California has not only the longest history of medical marijuana but has also had the most liberal indications for recommending its use, including "cancer, anorexia, AIDS, chronic pain, spasticity, glaucoma, arthritis, migraine, or *any other illness for which marijuana provides relief*" [author's own emphasis]. Studies of the state's medical marijuana users and dispensaries serving them are hampered by privacy concerns due to federal prohibition of all marijuana use and medical standards of confidentiality. One study gathered data regarding 1655 individuals seen during three months in 2006 at nine medical marijuana dispensaries throughout California.[111] Almost 73% of customers were male and over 50% were 35 years old or older, which is considerably older than the 2006 National Survey of Drug Use and Health age of ~28 for adults reporting purchase of marijuana in the previous month. Most medical marijuana users cite more than one symptom being treated. The most frequently mentioned symptoms were pain relief (82.6%), improved sleep (70.6%), relaxation (55.6%), muscle spasms (41.3%), headache (40.8%), and relief of anxiety (38.1%).

California's Compassionate Use Act, passed by a referendum in 1996 (55.6% to 44.4%), dealt an important blow against the federal government's rigid and stubborn resistance to scientific information confirming the potential usefulness of cannabinoid-based medications. California's action challenged America's misguided and ineffective strategy of waging a War on Drugs (and ultimately on drug users), and no coherent strategy has yet emerged in response to this challenge. But there is no doubt that California failed to provide adequate guidelines and regulations for its burgeoning new industry. As a result, the glee of newfound freedom to grow and sell marijuana, and to

make money doing it, quickly led to perversions of the medical marijuana system most voters envisioned. Cannabis expositions developed with "nurses" sporting pink uniforms with miniskirts inviting attendees into evaluation cubicles where doctor's recommendations were available on request, which enabled "patients" to purchase their "medicine" on site. Advertisements in alternative newspapers touted samples of "cosmic cocktail" medical marijuana available with recommendations by physicians at "potdoc.com."

The Medical Board of California guidelines[112] for physicians recommending marijuana for medicinal use include the following:

- *Physician-Patient Relationship*: established prior to providing a recommendation
- *Patient Evaluation*: including history, physical examination, and diagnosis
- *Informed and Shared Decision-Making*: including a discussion of risks and adverse effects
- *Treatment Agreement*: including goals for evaluating treatment effectiveness and an "exit strategy" for discontinuing cannabis use in the event termination of cannabis use becomes necessary
- *Ongoing Monitoring*: including treatment plan modifications as needed
- *Medical Records*: should include the following
  - ✓ The patient's medical history, including a review of health risk factors and prior medical records as appropriate
  - ✓ Results of the appropriate prior examination, patient evaluation, diagnostic, therapeutic, and laboratory results
  - ✓ Other treatments and prescribed medications, including a review of the Controlled Substance Utilization Review and Evaluation System
  - ✓ Authorization, attestation, or recommendation for cannabis, to include date, expiration, and any additional information required by state statute
  - ✓ Instructions to the patient, including discussions of risks and benefits, side effects, and variable effects
  - ✓ Results of ongoing assessment and monitoring of patient's response to the use of cannabis
  - ✓ A copy of a signed treatment agreement, including instructions on safekeeping, and instructions on not sharing cannabis

What the Medical Board often gets, instead, are pot docs aggressively advocating for the marijuana industry. Some are enthusiastic about the value of this previously forbidden medicine while others are guided by libertarian beliefs, personal experience with marijuana, or easy financial reward for simply doing people a favor. However, from a medical perspective, any doctor that prescribed Prozac for any reason in any dose desired would be considered a highly unethical shill for Big Pharma. In a similar vein, recommendations for medical marijuana are often given for any reason in any dose of whatever is sold at dispensaries without any guarantee of purity (until recently). It took California over 20 years to pass regulations requiring dose, contents, and purity to be tested and provided. As far as the Medical Board's "standards of medical practice" are concerned, very few, if any, doctors have been investigated for failure to meet them.

The increasing popularity of edible products such as gummi bears infused with THC and/or CBD sold both in medical dispensaries and retail outlets is circling us back to earlier times. In the 1860s, the Gunjah Wallah Hasheesh Candy Company made maple sugar

hashish candy, which soon became one of the most popular treats in America. For 40 years, it was sold over the counter and advertised in newspapers, as well as being listed in the Sears-Roebuck catalog, as "A most pleasurable and harmless stimulant – Cures Nervousness, Weakness, Melancholy, &c. Inspires all classes with new life and energy. A complete mental and physical invigorator."[113]

The more things change . . . the more they stay the same. People still want what they want. People still suffer illness and infirmity. And people still try to make money by selling what pleases. The marketing of real medicine in a fashion reminiscent of snake oil still has charm.

The problem underlying the current system of medical marijuana is that the public's health and physicians' integrity are protected only when "medical" means "based on scientific principles." Health food stores and vitamin shops are permitted to make general claims (e.g., "*may* improve heart health" [author's emphasis added]) as long as they do not claim to make medical diagnoses and sell potentially harmful products if misused. Public safety requires regulation of more powerful compounds and licensing of professionals trained to use them properly. The medical marijuana industry cannot ultimately have it both ways, although regulations seem to permit this. While California initially required marijuana to be designated as either medical or recreational from the moment it was planted, it now permits the designation to be made at the retail level on the basis of supply and demand, which formally acknowledges no difference exists between "medical" and recreational marijuana. How can marijuana, in its multitude of forms and derivatives, be both a powerful medicine with potentially addictive side effects, and just another herb on alternative medicine shelves that "may improve" this or that symptom? The scientific evidence is falling overwhelmingly on the side of it having legitimate medical benefit *and* the potential for addiction? The time is not far off before cannabinoid-based medications, including even marijuana when appropriate, will become the purview of medical professionals trained to diagnose and treat illness with the most effective, safe, and agreeable medicines and pharmacists trained to provide objective information and double check for potential interactions with a patient's other medications. Such interactions are known to occur due to THC and CBD's interactions with the liver's cytochrome P-450 enzyme system. Though not generally causing clinically significant impacts on other drugs metabolized by P-450, a huge variety of common medications are eliminated through these liver enzymes. Further study of specific drugs and individual human genetic variations still need attention.[114]

Until cannabinoid-based medications, including marijuana, are truly integrated into scientific medicine, we will have to tolerate many people calling marijuana medicine as a cover for getting stoned every day. Chapters 14 and 15 explore how current marijuana laws developed and how some states and other countries are trying to achieve more rational and effective marijuana policies.

Alice

The elderly, frail woman stubbornly clung to life as metastatic breast cancer was gradually winning the battle. Her opiate pain medication was working but dulled her mind to a distressing degree, caused profound constipation, and was starting to suppress her breathing. She stridently objected to the suggestion that a low dose combination of THC/CBD might permit a reduction in the opiate dose, and therefore relief from its side effects, while

maintaining adequate pain relief. She was morally opposed to any use of "marijuana" because she said it had ruined her grandson's life. Alice began relaxing when her doctor explained how research had proven THC and CBD resemble her natural brain chemistry in much the same way morphine resembles her endorphins. More importantly, her nurses reassured Alice with several stories of cancer patients they had seen be helped by tinctures produced from the cannabis plant. The word "tincture" is calming and using the words "cannabis plant" instead of "marijuana" was also helpful. Alice cautiously agreed to try the THC/CBD and was able to use less opiate medication during the final days of her life without any loss of pain relief. Although she still did not feel her mind was entirely clear, she was more interactive with her family and had improved appetite toward the end. The balm provided by a combination of cannabinoid and opioid pain relief had fewer side effects than opiates alone, but sophisticated patient education was required for Alice, a lifelong marijuana opponent, to feel comfortable enough to give the combination a trial. She was lucky that her physician and nurses knew the facts and how to tailor their presentation to her.

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Chapter

11

Understanding and Encouragement

Compassion for Marijuana Use Disorder Sufferers

Most people who use marijuana enjoy the experience and are effectively going about their lives. But there are others who crash and burn, or at least smolder, especially young adolescents who use marijuana too heavily for their own good. There are also young adults whose failure to launch may not be solely caused by marijuana, but pot certainly aids and abets their compromised success. And there are those few who experience wrenching psychosis and who might not have visited this private hell if they had not overused pot.

Because marijuana does the most harm to those who begin using it seriously as young adolescents, much of this chapter will address parents. The principles suggested for dealing with an addicted adolescent generally apply to adult partners and friends as well, but the dilemmas faced by parents tend to be more excruciating and immediate.

My heart goes out to tormented parents, often wracked with pain, guilt, and a sense of failed responsibility uncomfortably mixed with anger, blame, profound frustration, and resentment. Too often couples find themselves torn apart, distanced from each other by passionately held opposing ideas for how to help their child, or even if help is needed. They often careen from rescuing their child from the consequences of their addiction to imposing harsh punishments in an effort to "wake their child up" to recognize the reality of what they are doing to themselves. The excruciatingly urgent desire to help may alternate with demoralized collapse into apathetic helplessness. Parents may come to doubt their own self-worth as they experience a deeper level of impotence than they had previously known existed. If they are ever going to provide a healthy home for their child to deal with the harm being done to him or herself by marijuana, parents often need help themselves to regain their own footing and a sense of parental authority.

It is altogether too easy to repeat the mantra to parents, "It's not your fault." But do we really mean it, and is it always true? Parents contribute both positively and negatively to the world their children know most intimately and consistently. When that world is filled with over-indulgence and lack of discipline, tension and discord, chaos and unpredictability, substance abuse or child abuse, we stack the deck against a child's navigating through adolescence successfully. When that world is filled with relatively unconditional love, acceptance, clear expectations, firmness, and warmth, we lower the risk of a child's getting off track in the journey toward adulthood. We wield powerful influence, for good and for bad, on the course of our children's lives and each of us is called upon to look with rigorous honesty at what we teach by word and especially by our own actions.

But there are serious limits to what can be controlled in a child's life. We have absolutely no control over their genetic makeup. Each of our children begins life with a DNA blueprint, one quarter of which comes from each grandparent. None of us can be held responsible for the genes governing temperament, emotional and cognitive abilities, attention deficits, or a myriad of other challenges that may have passed through us to our children. This includes any combination of genes that increase their susceptibility to addiction. Each individual, including both ourselves and our children, cannot be blamed for the cards they are dealt, yet we all must assume full responsibility for playing those cards as well as possible.

We raise children to be independent, which is a good thing because independence is expected of our society. Although we have considerable influence, none of us can dictate what our children think, what they feel, how they see their place in the world, what risks they take, and which they avoid. While sometimes we might want to have complete control over our children's minds, we also do not want to turn them into mere drones robotically following our every order. That would be neither possible nor desirable. If that degree of control over another person were possible, we would have no freedom ourselves and would be over-burdened by total responsibility for others' happiness.

The largest community focused on concern for a loved one's harmful involvement with marijuana (or alcohol and other drugs) is found in Al-Anon Family Groups, which condense their awareness of the limits on our power over other individuals into the word "powerlessness."[1] Many people desperate to help a child they are watching swirl down a drain with marijuana initially rebel against that word because they misinterpret it to mean there is nothing they can do to help the situation. "Powerlessness" is only intended to mean that we have no direct control over what another person thinks or wants. We only have control over how we view someone's addiction and how we try to help. When the child we are concerned about is under 18 years old, parents also have powerful legal authority, but still remain powerless to make a child want what the parents think he or she should want. All too often, parental efforts to *force* a child to behave are met with stiffened resistance to being controlled. All most of us need to understand this dynamic is to remember our own efforts as adolescents to achieve freedom from parental constraints.

The wisdom of Al-Anon lies in helping people stop making things worse by increasing their vain efforts to control what is inherently uncontrollable. This releases them to turn their energies in more useful directions. (Public policy would be improved by also incorporating this wisdom, which is discussed in Chapter 15.) Two important shifts in attitude stem from accepting that there is no perfect thing you can say, or do, that would magically work, that would make someone recover from their addiction. First, you are

relieved from your sense of failure. You no longer believe it is your fault for not finding the magic formula for someone else's success. Second, by accepting your powerlessness to *make* someone behave the way you think they should, you communicate the realistic subtext that the responsibility for recovery from addiction lies solely on the shoulders of the person who is addicted. In what often feels like a paradoxical twist, abandoning the responsibility for managing another person's life for them conveys respect, while feeling responsible for managing their life conveys a disparaging view of them as immature and incapable.

I counsel parents to strive to understand and encourage their addicted child. Understanding takes many forms. First, it is important to understand that once addiction has developed, a person's brain is not working properly. This does not mean they are unable to mount full, and often cogent, defenses for their behavior. It merely means that their brain's reward system has been captured – hijacked – by marijuana. The *salience* of marijuana has been elevated above most, if not all, other potential rewards. The concept of salience is of vital importance here.

When our hippocampus, amygdala, and nucleus accumbens simultaneously attach memory, emotion, and reward to a stimulus, powerfully drawing our attention to it, we say the object or event has salience, or prominence. Marijuana is intrinsically enjoyable for most people and intensely stimulates dopamine in the reward system. When salience is generated from bottom-up, meaning by physical changes in the brain's reward system, people become highly motivated to continue using. The mental experience of this brain-driven urge is to "want," or "desire," the rewarding chemical. Reason is distorted to rationalize daily pursuit of the brain reward offered by marijuana. Pot addiction thus results as much from a brain condition (some would say "brain disorder") as from an individual's psychology. When it is rooted in both, the attraction can be not only irresistible, but there may be no desire to resist it.

Parents need to understand that sometimes their child has become powerless over the impact marijuana has on their brain. No amount of tough love, punishment, or even unconditional love can return their child's brain to normal functioning until he or she abstains from using pot.

Encouragement for a marijuana-addicted child takes patience – often more patience than a parent has on his or her own. Our better angels often need support and encouragement from others locked in the same struggle to remain as patient and persistent as the situation requires.

Encouragement calls for us to remain connected to what is good in a child. It means refusing to disparage who they are and to avoid rejecting them in the myriad of ways they sense our judgment. By embodying the belief that a child can make better choices for themselves, we promote the courage they need to change course, if they ever choose to. Encouragement is felt when we offer the support a child needs to make and act on different choices.

Encouragement does not mean being passive or permissive. The following experience with an equine therapist taught a couple all they needed to know about how to understand and encourage their teenage daughter. They were given a halter and told to put it on Paint, a horse contentedly munching grass on the other side of a small pasture. They walked calmly toward Paint, trying to look as friendly and nonthreatening as possible. Then they petted and stroked the horse's flanks and neck. Before the horse suspected their intent, the father attempted to pull the halter over its head. No cowboy, the man

fumbled with the confusing straps long enough for the horse to realize what was happening and trot away.

"You had a chance, but you didn't have a clear plan," the therapist said. "The halter needs to go over the nose first," he instructed.

Now Paint was wary when they approached. The father told his wife to circle around and distract the horse. Then he rushed up, threw his arm around its neck and tried to wrestle the halter on. This time Paint reared up and almost knocked the man over before running off.

"Careful," the therapist cautioned. "You're not going to overpower 1200 pounds of good horse flesh. Besides, she's a prey animal and sees you as a predator, kinda like your kid, wouldn't you say."

"We need sugar cubes," the woman exclaimed. She ran into the barn and returned with a handful of sugar and a couple apples. Together the couple worked to get Paint eating out of her hand with the halter draped on her arm. Slowly they moved the halter up, parceling out one sugar cube at a time to keep the horse occupied. At the last instant Paint jostled the woman's hand roughly. The sugar fell to the ground. Paint pushed the halter away, bent to gobble every last cube, and then strutted away disdainfully.

"I guess bribes don't work, do they," the therapist laughed. "How many lost cell phones have you bought her?"

The couple looked discouraged. Finally, they turned to the therapist and asked what they could do. "At last," he replied with mock exasperation. "I thought you'd never ask for help. You've lived in the city your whole lives and still thought you should know how to work a horse instead of consulting someone with experience . . . Look at her. What's she doing now?"

Paint had returned to contentedly eating the lush grass.

"What should we do?"

"Well, you can't force her to do what *you* want, but you can keep her from doing what *she* wants."

With that the man began an exhausting routine of chasing Paint away whenever she lowered her head to grab at the grass. When he began to tire, his wife took over for him. You could see Paint's frustration growing. She began letting them get closer before running away, then stopped running and let them pet her. When her head started down toward the grass, one of them put an arm under Paint's neck and pulled her up again. Dad showed Paint the harness. Paint bent again toward the grass but was jerked back up before getting a single blade. They gradually let the horse's head lower as Paint gradually let the harness be slipped on. At the moment the strap was snapped on she was allowed to eat the grass. Everyone was happy.

"You figured out what Paint wants, not what you thought she should want. Then you kept her from getting it unless she cooperated."

"Yea, but it took a lot of work."

"Well, nobody ever said parenting was easy. Would you rather keep doing things your way, failing, and then blaming your daughter for being obstinate? Or would you rather take the harder path that has a better chance of success. I understand wanting to force your solution to work. I understand wanting to be in control of your kid. But your kid is ultimately in control of the choices she makes. Not you. You have to offer different choices – ones that don't *force* her to change but that make it harder for her to remain the same."

"All she wants is to smoke dope!" they both shouted at the same time.

"If that's truly all she wants, you won't be able to brainwash her into anything different. But I think she wants more than that. I think she wants to feel capable and independent. Smoking pot is the only thing you have to make more difficult for her."

I know this cute equine therapy scenario sounds oversimplified, but it does embody several simple truths. No matter how much children are rebelling, most of them still would prefer to feel their parents' love and respect. And no matter how devoted they are to using marijuana at any cost, they also want their freedom and their cell phone. But most importantly, the vignette illustrates that we are powerless to force our children to think and behave the way we want them to. Ultimately, this is a good thing. It would be a disaster if we had the power to extract thoughts and feelings from their minds and implant the ones we want them to have. Then we would be raising robots, not human children. We would be denying them the respect and autonomy that are necessary for free will to exist. And we would be forever responsible for how they lived their lives, meaning we would probably make the same mess of things for them that we have in our own lives. No, it is a far better thing for our children to have minds of their own even though this may put the fear of God in our hearts from time to time. And even though some are willful to their own serious detriment. Like 1200 pound horses that can feel prey to our efforts to control their lives, our kids have the power to think and feel for themselves, and often the need to prove this to themselves over and over by their actions.

The fact that we are powerless to force a child to think differently does not mean that parents have no power. They have the power to understand, to empathize, and to encourage. They have the power inherent in being the most consistent and loving part of a child's environment. They have the power to determine the family's values, but only to the extent that their own lives embody these values. They have the power of more resources, including authority over the family's home. And they have legal authority over children under 18.

Understanding includes more than the empathic pat on the back we give a child when we say we know how it feels to lose a game. When dealing with a child who is harmfully involved with weed, understanding means taking the time to know enough facts about marijuana that we have the internal authority necessary not to be buffaloed by their arguments, misinformation, justifications, and rationalizations. Any parent who knows the facts will not be taken in by the following defenses commonly offered by their child:

1. "Everyone uses weed."
   Wrong; even among the highest-use age group, non-use is as normal as use (among 18–25-year-olds, only one out of five used marijuana during the past month).[2] The truth may merely be that nearly everyone *in your child's peer group* may be using – a self-selected sample.
2. "It can't be harmful because it's natural and organic."
   Organic is good but no guarantee of safety. Death cap mushrooms (*Amanita phalloides*) are natural and organic. And when no quality control of testing monitors marijuana cultivation, it is impossible to know what chemicals have been used during cultivation. (Steep Hill Laboratory found high levels of pesticides in 93% of samples purchased in the LA area in 2017.[3])
3. "No one ever died from a marijuana overdose."

Probably true, except in a car crash, but death is a very low bar for determining safety. On the other hand, many relationships, dreams, and aspirations have died from overusing marijuana.

4. "It makes me feel better."
   So does cocaine, but that does not make it the wisest choice for lifting your mood. There is a fundamental difference between symptom relief and healing. The great Rastafarian Bob Marley may have sung "Let's get together and feel alright," but most people want to feel better than just alright. His lyric sounds like someone in withdrawal wanting to feel "normal" ("alright") again. Feeling truly good comes from doing really good things.
5. "I feel more present when I'm stoned."
   Feelings are not always accurate measures of reality. Staci Gruber's research shows that the brains of marijuana users respond less to subtle emotional cues than nonusers. A lack of emotional presence impairs relationships. Hester and Nestor's work on unawareness of errors during a go/no-go task is a measure of not being fully present.
6. "Marijuana is not harmful."
   That is not what science tells us. There is clear evidence that persistent overuse of marijuana alters the assessment of risk, diminishes executive functioning, especially in early onset users, and is associated with significantly lower educational achievement and income later in life. It can even lower IQ and provoke schizophrenia in a few unlucky people.
7. "But it's my medicine and I have a right to have my medicine."
   Of course, people have a right to receive effective medication, and physicians have the responsibility to make objective decisions that weigh benefits and side effects of any medication in light of each individual's disease condition. What illness do you have that requires medication? Let's get it evaluated properly and treated as effectively as possible.
8. "You have a drink in the evening. What's the difference? Besides, alcohol kills far more people than pot ever will."
   Whoops . . . Maybe it is time for a little introspection on the parents' part. If it is not healthy for an adolescent to use a pharmaceutical aid for relaxation, what *does* make it acceptable for adults? I leave the answer to each individual to determine their own values and set their own priorities within the context of their own family's circumstances. But this defense of marijuana use deserves to be faced seriously and answered respectfully.

The goal of listing adolescents' common arguments for being allowed to use marijuana is not to give parents ammunition to prove a child wrong, but rather to reinforce the sense of authority parents need to stand up for their own perspective and values. It is often best not to engage with an adolescent's arguments, but rather simply to have enough facts that are incompatible with their logic not to be swayed from your own truth. Too often, debate is interpreted by a child as negotiation, as though if she or he argues forcefully enough parents are open to changing their minds.

Understanding and encouragement require work on the part of parents. The ability to embody authority, whether an adolescent is willing to grant parental authority or not, stems from a firm grasp of the facts rather than relying on opinion alone. A deep sense of

authority is needed for parents to communicate their values clearly and unambiguously. It also requires an acceptance of the limits of power that respects the autonomy of a child's mind. Authoritarian approaches that demand obedience in feeling, thought, and behavior rarely succeed. In fact, authoritarian styles usually end up pitting a parent's ego against a child's self-esteem. Some children go underground and feign compliance; some have their spirit broken; and others openly rebel.

Parental authority also stems from parental integrity – living a life that embodies what you hope children will learn. We teach more by our example than by our words. In fact, asking children to do as we say and not as we do is invariably seen as hypocrisy by youth, as well it should be. Organizing social functions, celebrations, and relaxation around alcohol while condemning a child's use of marijuana in similar events destroys whatever authority and respect you need to influence their decisions. This does not mean that alcohol, or even marijuana, cannot be part of a parent's life, but rather that it not be used unthinkingly, unconsciously, or without examination. The goal for our children is that they not harm their lives, even in small ways, by overusing marijuana. The same attention to potential harm must also apply to parents if they want their children's respect.

Ultimately parents are responsible for carrying values that safeguard the integrity of the family. Behaviors that threaten the sanctity of the family, both from without and from within, need to be identified and opposed. When marijuana becomes the central organizing principle of an adolescent's life, both the adolescent and the family are threatened. Marijuana is the threat from without. The adolescent's behavior is the threat from within. Parents very often have difficulty getting on the same page about how to view, and what to do about, the problem. Tension and conflict can erupt within the couple. Younger children may sense the tension, suffer from parents' attention being over-focused on an older sibling's problems, or even be pressured to withhold a sibling's secrets from their parents.

When adolescents refuse to stop using marijuana despite their parents' firm insistence, it is time to make their use more difficult – metaphorically to keep the horse from being able to leisurely munch the grass. I usually recommend a process of contracting for responsibilities and privileges with progressively more consequences for failure to live up to the contract's agreements.[4] Parents present a written contract to their child with measurable responsibilities supporting the family that include chores, meals, curfew, schoolwork, abstinence from marijuana, alcohol, and other drugs, and sometimes arrangements for urine drug screening. In return for agreeing to the contract, the adolescent gets the privileges outlined, including computer and videogame time, cell phone, allowance, use of the car, and overnights with friends (contingent on parent to parent contact). The contract needs to spell out ways parents will support their child (e.g., pledging abstinence themselves for the length of the contract, seeking consultation themselves with an addiction therapist to assess whether their concern is excessive, and providing a counselor for their child to talk to about the contract if they wish). Contracts need to clearly spell out the consequences of failure to sign the contract (gradual loss of privileges), and refusal to cooperate with urine screens or positive screens (e.g., evaluation by an addiction expert, weekly counseling or therapy, or entry into an intensive outpatient treatment program).

The contracting process is likely to generate heat, so it is important for the parents to be united and come more from a place of love than anger. Whatever negotiations their child tries should be viewed as their negotiating with him or herself. What choices are

they going to make, and what consequences will their choices entail? Because a written contract will be seen as a change in course by parents, many children will have to test whether the consequences are merely threats or real. When they lose use of their cell phone, it gets real. Anger may escalate, but parents need to understand that their actions are finally speaking louder than words.

I am not suggesting that any course of action is guaranteed to succeed. There are no such guarantees with addiction. The goal should be for parents to keep their integrity and not be drawn into useless shouting matches. Power struggles are worse than useless. Both sides are damaged and the struggle takes center stage rather than the addiction and concern for the addict. Families have norms, and addiction falls outside the norm. "How can we help?" needs to be the message from parent to child.

Finding the equanimity to sustain such an accepting and respectful message while being disparaged, or even hated, by your child is tremendously difficult. Maintaining awareness and acceptance of the fact that your child, awash in the glory of their own free will, is the only one who can choose to abstain from marijuana requires faith in your child. Many parents are able to sustain an attitude of understanding and encouragement for their child to make healthier choices only with support for themselves. Al-Anon Family Groups provide a community of people with loved ones who suffer addiction. They stand ready to share their experience, their strength, and their hope with others. While no ready answers or guarantees will be found at these free meetings, an abundance of wisdom and support is available.

Another benefit of Al-Anon meetings is hope – realistic hope. Chapter 4 (on Epidemiology) reviewed data regarding the tendency of people to age out of excessive marijuana use. Al-Anon is filled with stories of adolescents who realized the negative impact of their alcohol and other drug use early enough to rescue their potential. When parents take adolescent use of marijuana seriously, Al-Anon can help them create a family atmosphere that is conducive to early recovery rather than throwing the gasoline of their own anger and frustration into the fire that is driving a wedge between them and a child in trouble with marijuana.

Just as airplane passengers must put on their own oxygen mask before helping with their child's, parents of marijuana addicts must maintain their own health in order to be able to help their child. They must heal their hurt feelings and wounded pride in order to be able to respond reasonably rather than react from fear and anger. They must heal from lost expectations to deal with the reality of their child's addiction. And they must heal from the grandiose hope that they have the power to force their child, whether by punishment or unconditional love, to change in the direction they prescribe.

Marcus and Maddie

Separated for a year and preparing for divorce, Annie's parents were bereft and furious. More accurately, Maddie was bereft and Marcus was furious. Their 15-year-old daughter, Annie, kept breaking her promises to them to stop using marijuana.

"What bothers you the most about her marijuana use?" I asked Annie's parents when I had all three of them together.

"I'm afraid Annie can't stop," Maddie said tearfully.

"I keep trying, but it's really hard," Annie seemed to be pleading for leniency.

"I'm sure it is," Maddie said at the same time Marcus pronounced, "Then you're not trying hard enough."

Annie turned on her father angrily. "You don't understand."

He continued, "I understand you like staying at your mother's because she lets you get away with whatever you want . . . I don't let you get away with smoking when you're with me."

"You're so stupid. I just hide it better when I'm with you," Annie burst out. I wasn't sure she really wanted her father to know this, but her defiance was pushed to the surface by Marcus's belief he could control her.

"Marcus," Maddie interrupted, "won't you please try Al-Anon again?"

"I don't buy that crap about being powerless. If you're still using when you're with me," he turned to Annie, "then I'm going to keep trying harder until I stop you."

"Let's step back a second and look at what everyone wants here," I said.

Marcus jumped in. "I'm tired of Annie not minding me and living by her own rules. I want her to stop using pot and I'm willing to do whatever is necessary to stop her."

"So, Marcus, you are interested in two things. You want to be minded, and you want Annie to stop using pot. Right?" He nodded agreement. "Is it more important for you to feel minded or for her to stop using? If you could have only one, which would you want?"

"If she minded me, she would stop."

"But if you could only have one or the other – feeling minded or her stopping – which would you choose?"

"Her stopping, I guess. But . . ."

I didn't give him time to continue. "OK, how about you, Maddie?"

"I want her to realize she'd be happier in the long run if she didn't smoke marijuana."

"But I do know that, Mom. I'm just not paying attention to it all the time."

"Annie, why do you think you're not paying attention to your own better judgment?" I asked, leaning toward her.

" I don't know . . . Maybe 'cause I'm still young and foolish sometimes." It was simultaneously a rationalization and the truth.

"You can say that again," Marcus said bitterly.

Annie stiffened, but before she could speak, I challenged her father. "That doesn't feel very encouraging, Marcus. It's more important for Annie to realize the truth of what she said than for you to know it. I'm impressed Annie is able to consider the possibility she may be acting foolishly, and then to actually say it out loud here. I think she may be building a stronger foundation for getting straight than your effort to control her ever will."

Maddie reached over to take her daughter's hand, but spoke to Marcus. "I think our job is to listen to her struggles, clearly state our values, and encourage her better judgment. Can you have faith she already knows the right path?"

Annie made eye contact with her mother and said, "Thank you, Mom."

Marcus took a deep breath, half out of resignation and half gathering the courage to say, "I guess the most important thing, Annie, is for you to focus on not breaking promises to yourself and not to us."

"I couldn't have said it better, Marcus," Maddie encouraged.

Notes

1. Al-Anon Family Groups. *How Al-Anon Works for Families & Friends of Alcoholics*, Al-Anon Family Groups, 1995.
2. Substance Abuse and Mental Health Services Administration. *Key substance use and mental health indicators in the United States: Results from the 2017 National Survey on Drug Use and Health*, (HHS Publication No. SMA 18–5068, NSDUH Series H-53). Rockville, MD, Center for Behavioral Health Statistics and Quality,

Substance Abuse and Mental Health Services Administration, 2018. www.samhsa.gov/data/report/2017-nsduh-annual-national-report (Accessed March 25, 2019.)

3. M. Classer and J. Grover. *Pesticides and Pot: Lab Results, Company Statements*, NBC4 News, NBCUniversal Media, 2019. www.nbclosangeles.com/news/local/Pesticide-Laced-Pot-Lab-Results-Company-Statements-I-Team-414526923.html (Accessed March 25, 2019.)

4. D. Schaeffer. *Choices and Consequences*, Hazelden Publishing, 1998.

Chapter

12 Principles of Motivational Interviewing

Clinicians who hope to modify patients' unhealthy behaviors face the same limitations and potential frustrations encountered by family members and friends of substance abusers described in the previous chapter. Many of the emotions felt by frustrated parents may also be experienced by clinicians. Despite years of professional training, clinicians have to deal with the same entrenched and obstinate habits, defended with the same irrational fervor, or locked in place by the same collapse of hope. It does not matter if people are family or patients, helping them change encounters the same barriers.

Few people enter medicine or the mental health professions in order to specialize in treating alcoholics and drug abusers, and few training programs offer much education on addiction. Learning how to diagnose and treat heart attacks and depression, to fix broken bones, and ease people through traumatic events strikes most clinicians as more immediate and, quite frankly, more interesting than dealing with what appears to be the self-inflicted suffering of addiction. And yet, there is ultimately no way for all variety of clinicians to get away from dealing with the effects of alcohol and drug use. Alcoholics break bones and marriages. Tobacco users have heart attacks and leave grieving families. Obstetricians and pediatricians must constantly be on the lookout for the impact of parental alcohol, tobacco, and drug use on their young patients. While few clinicians directly treat addiction, everyone has the opportunity on a daily, or near daily, basis to be the gatekeeper into addiction treatment for their patients who need it. I would propose that this is not merely an opportunity, but rather an obligation.

Physicians, psychologists, family therapists, social workers, and counselors of every variety face the same situation. Learning their craft is difficult enough without having to deal with what are often seen as the less interesting problems presented by drug and alcohol abuse. The perception that addiction gets in the way of treating the problems clinicians train to treat is accurate. Addiction usually has to be dealt with before being

able to treat pancreatitis, depression, psychosis, or marital strife. A distressing number of problems are complicated by patients' harmful use of substances. It is precisely because of the high incidence of comorbidity found in physical and mental health disorders that all clinicians should feel obligated to become skilled at recognizing and referring substance abusers to specialized treatment if they are unable or unwilling to provide it themselves.

One reason many clinicians shy away from shouldering this obligation is the impotence they feel in the face of what often seems to be an impenetrable façade presented by heavy users. There are so many problems to address, and so little time, that often little more than a brief injunction to cut down their use is given. Fortunately, a far more effective approach can easily be mastered and incorporated into your practice. The principles of motivational interviewing, when combined with a basic understanding of the stages of change, offer clinicians a pragmatic framework for talking to patients with substance abuse issues.

The Stages of Change

Too often people declare that failed attempts by substance abusers to get sober are because "they were not ready to change – they have not *hit bottom* yet." This leaves the process of change as a complete mystery, entirely beyond the influence of those attempting to help addicts. It suggests either trying to "raise the bottom" through education about the negative effects of alcohol and other drug use, or permitting further negative consequences to occur in order to produce enough pain that the bottom is reached. Understanding the stages of change has largely replaced this simplistic view of change within addiction medicine.

The psychologist James Prochaska described a general model of change after conducting a comparative analysis of the process of change within a multitude of therapy systems as well as when it occurs spontaneously. In a pioneering study of 872 subjects changing their smoking habits on their own, self-changers followed the same process of change as individuals in formalized smoking cessation treatments. Together with his colleague, Carlo Di Clemente, they began publishing a series of papers in the early 1980s introducing and developing the stages of change model.[1,2,3] Change is a process and understanding where a patient is in the process instructs clinicians regarding responses that might promote advancement to the next stage. An analogy could be made to advising your partner how to get their car out of a snowdrift. It is best not to begin pushing the car before shoveling snow away from the wheels, and best not to begin shoveling before putting on gloves and becoming familiar with whether the car is front or back wheel drive. Of course, encouraging your partner to get out the gloves and shovel is wasted effort if s/he has already decided to cancel plans to drive somewhere.

There are five identifiable stages of change in the classic model, each with its own dynamic and potential for helping someone proceed to the next stage. Just as with the stages of grief outlined by Elizabeth Kubler Ross, movement through the stages of change is not always a straight line. People can bounce back and forth between stages, vacillating in their motivation and circumstances, sometimes indefinitely, sometimes only briefly. Prochaska and Di Clemente's model does not address the pace of change – only the process. But their outline tells clinicians clearly where to place the emphasis of their interactions with any given patient.

Stage one, **Precontemplation**, does not appear at first blush to be a part of the change process. Precontemplators are not currently considering change. They are not open to new information and seem to practice an "Ignorance is bliss" philosophy. At other times they might defiantly defend the logic of their behavior, or simply their right to be who they are. There are still helpful strategies available to clinicians during the precontemplation stage. Being a nag is not one of them. It is important to avoid pushing precontemplators in ways that only increase their defenses. Instead, it is useful to validate their lack of readiness and clarify that the decision to change, or not, is theirs. Look for teachable moments (e.g., the first diagnosis of hypertension in a smoker, a divorce due to alcoholism, or falling grades in a young marijuana user) to explain and personalize the risks known to be associated with their level of use. Re-evaluation of current behavior and self-exploration are temporarily more likely if factual information about risk is provided at moments negative consequences are being experienced. For example, a study of brief intervention in a pediatric emergency department provided 14–21-year-old marijuana users with an assessment, resources, written advice, 3- and 12-month appointments, a 20-minute structured conversation conducted by older peers, and a 10-day booster telephone call. Results at the 12-month follow-up demonstrated an increased likelihood of being abstinent for the past 30 days and greater reduction in days used.[4]

Finally, do not ever forget the power of being confused and not understanding a precontemplator's behavior. No matter how elaborate a patient's rationalizations for self-destructive behavior may be, clinicians should feel comfortable registering an inability to comprehend their logic. Sometimes it plants a seed when we are open about simply not getting why a patient continues unhealthy behavior before we pass on to the next topic.

Stage two, **Contemplation**, begins when a window opens to awareness of the negative impact of current behavior. This is a time when ambivalence about change and "Sitting on the fence" starts. As with the precontemplation stage, it remains important to continue validating that the patient is not convinced change is necessary and the decision whether to change is entirely up to them. The goal at this point is to increase the ambivalence a patient is experiencing. Clinicians can become a bit more directive at this point, increasing a patient's awareness of the adverse impacts of their behavior by connecting perceived problems to the influence of their substance use. It is a time to encourage evaluating the pros and cons of change and to promote new, positive expectations for potential benefits of change. For example, the young marijuana user with falling grades may be more interested at this point in research on the impact of marijuana on verbal memory and delayed recall. Abstinence will soon reverse the difficulty with memory, if they so choose.

Stage three, **Preparation**, is present when people are planning to change in the foreseeable future. They may begin "testing out" actions that could lead to change. Clinicians can help by identifying potential obstacles and assisting in problem solving and gathering social support. Sometimes encouragement for small initial steps can be given. This is also a stage when discussion to clarify a patient's values and goals can be helpful. For example, the student with falling grades may still hope to go to a good university and enter a lucrative or meaningful career. Providing information about lower academic achievement and income in chronic marijuana users pits their continued use against their own goals. Or an athlete might see that marijuana's interference with learning from mistakes violates their goal of making it into the starting lineup.

A clinician needs to know each patient's personal values and goals in order to know which data will be most impactful. At the same time, asking about a patient's future hopes and dreams helps solidify the therapeutic alliance more than unremitting focus on marijuana use.

Stage four is **Action**, a time when new behaviors are practiced. Clinicians should focus on helping patients begin identifying and avoiding cues associated with old behaviors. Feelings of loss need to be acknowledged and compared to expected long-term benefits and future losses if the addiction continues. The use of social support to help deal with obstacles should be reframed as a normal avenue for self-efficacy. This is a time to encourage newly abstinent marijuana users to stick with other non-users in order to avoid situations and people who make relapse more likely. It is also a time to acknowledge the accomplishment of even brief periods of abstinence, using the comparison of withdrawal from tobacco and marijuana to give weight to the intensity of struggle being faced.

Maintenance is the fifth stage and requires continued commitment to sustaining new behavior. Clinicians should respond to maintainers by reinforcing a patient's internal sense of reward, sprinkled with encouragement to remember the negative impacts of their old behavior. It is also useful to begin discussing coping skills for preventing, or dealing with, relapse, when old behaviors are resumed. "Falling off the wagon" can be a time of deep discouragement, but clinicians can help to turn relapse into a call for new action, in part by treating relapses as a normal part of the process of change. There can be no relapse without there having been real change first. Patients need to be reminded of the preceding success and encouraged to identify triggers that led to the relapse. Clinicians can help them seek clues they had missed that preceded and presaged the relapse. There is an important lesson to be learned from every relapse, a nugget of information and self-understanding to be mined and used to develop even stronger coping strategies for maintenance of the desired change. Unless each relapse's lesson is discovered, the unidentified obstacle to maintenance is likely to trip the patient up again. Clinicians and patients can become partners in the detective work required after each relapse and the clinician's nonjudgmental attitude toward the relapse can help patients through their often harsh self-recriminations, shame for failing, and discouragement.

Motivational Interviewing

Motivational interviewing is more of a conversational counseling technique than psychotherapy, though it does incorporate some sophisticated therapeutic principles. It does not work to resolve the transfer of unconscious emotional biases and misperceptions from early life experience into current life. Instead, it helps patients work around these transferences in a very pragmatic effort to promote change in problematic behavior. The following overview of motivational interviewing should be seen as a description of how people change and how clinicians can best foster lifestyle changes toward increased wellness.

Utilizing the stages of change to guide the approach to promoting behavioral change introduces clinicians to one of the most essential principles of motivational interviewing, often described as "meeting patients where they are." While this facile phrase often sounds too "new agey" to many, it is really very hard-nosed in its pragmatism. It is useless to bang on locked doors, no matter how right you may be that the door should be opened.

Too much banging only bruises the knuckles and scares those on the other side. A more efficient approach is to identify and focus on the true points of leverage. The principles of motivational interviewing appeared in a paper by the University of New Mexico psychologist William Miller in 1983, the same year Prochaska and Di Clemente began writing about stages of change.[5] Miller combined with Stephen Rollnick to develop his framework further in the 1991 book *Motivational Interviewing: Preparing People to Change Addictive Behavior*.[6] Their work has had a profound impact on addiction medicine by shifting the focus away from resistance and denial in order to focus instead on ambivalence. Motivational interviewing moved clinicians away from confrontation and toward more cooperative strategies, which also entailed shifting clinicians away from the role of expert into a more patient-centered approach. In a simplistic analogy, clinicians switched from boxers trying to knock out denial to judo practitioners, going with patients' resistance to form an alliance that enables them to elicit and confront their underlying ambivalence. While all this might sound too squishy at first, the technique of motivational interviewing is eminently pragmatic and teachable.

Motivational interviewing is based on the following assumptions:[7]

- Ambivalence about substance use (and change in general) is normal and constitutes an important opportunity for change.
- Ambivalence can be heightened and resolved by eliciting intrinsic motivations and values.
- The alliance between clinician and patient is a collaborative partnership to which each brings important, but different, expertise.
- An empathic, supportive, yet directive, counseling style creates a relationship within which change is more likely to occur.

Ambivalence is both the obstacle to, and leverage for, change. Clinicians must view ambivalence as entirely normal in order to make it safe for patients to reveal and explore their ambivalent feelings. Friction is generated when clinicians view ambivalence as denial or resistance. Substance abusers are usually aware, at some level, that they are endangering themselves. They want to be rid of danger, but at the same time they want to continue using – to have their cake and eat it too. We all know how that feels in one form or another. It should not be too hard to empathize, except that many clinicians' clear view of the obvious harm done to a patient's health by their drug use can make it hard to reserve judgment. But such judgment can never be fully hidden. It ultimately evokes either shame or resentment, or both, in patients. The best way to cleanse ourselves of judgments that demean a patient is to dig deeply enough into ourselves to find ways that our own excessive eating, lack of exercise, overworking, or lack of attention to our family is obviously detrimental, and yet we continue the behavior. Ambivalence is normal and often accompanies compromises we feel justified making in our lives.

Five general principles guide the practice of motivational interviewing:[8]

1 Engagement Through Expressing Empathy

Empathy is the gateway to engaging people in a therapeutic alliance – the relationship that enables you to "hold" patients while they tolerate the discomfort of acknowledging how their old, familiar behaviors have harmed them. Empathy strives to understand, both cognitively and emotionally, the *meaning* of what another person says, and to effectively communicate that understanding, both cognitively and emotionally. While

any definition of empathy sounds complex and difficult, practicing empathy comes more naturally when you adopt a nonjudgmental, caring attitude toward others. A perfect example of empathy is when a parent exclaims, "Boom" after a toddler falls down. The child hears its parent's surprised tone of voice matching its own surprise at tumbling. The parent's emotional resonance is expressed clearly and spontaneously enough that the child knows they and their parent are together – bonded into a unified field. And they feel stabilized ("held") by that field. Emotional resonance does not mean that the other's emotional state is absorbed, but rather that it is correctly sensed, probably through the activation of mirror neurons, without critique or comment. The expression of emotional resonance means "I am with you; I get the emotional coloring of your experience."

Not everyone is equally skilled at empathy, but nearly everyone can improve if they work to clearly envision and honor the goal. At the bare minimum, empathy can be expressed by the technique of reflective listening (repeating the important portion of what patients have said, or guessing at what they are trying to say) described by Carl Rogers.[9,10,11] The key is listening, rather than telling. And when done properly, the respect and acceptance embedded in empathy creates an atmosphere of support and safety that makes it possible for patients to discuss their ambivalence at a deeper and more honest level.

Without good engagement, efforts to help someone change are likely to devolve into a struggle, as the clinician allies with the side of a patient's ambivalence that wants to change and the patient is left with only the side of their ambivalence that wants to maintain the old behavior. It is imperative to avoid this conundrum. Clinicians need to focus on listening to both sides of a patient's ambivalence without taking sides. Only then can the patient face the fact that the ambivalence is wholly theirs, lying entirely within themselves. The conflict is internal, rather than a fight between themselves and external forces trying to control them. Clinicians need to engage the whole person as patients wrestle with their ambivalence. Do not give them an easy out from the internal struggle by becoming the external embodiment of one pole of their ambivalence. The term "motivational interviewing" is sometimes incorrectly seen as an effort to supply motivation to a patient. The correct understanding of the term is that motivational interviewing attempts to identify the patient's own motivation to change and raise it more fully into awareness. Whenever I find myself having inadvertently entered into an argument with a patient, I remind myself that both sides of the conflict actually lie within the patient, and not between the patient and myself. This enables me to exit the disagreement, most often by acknowledging, "You may be right." It is remarkable how often this leads to the patient quickly acknowledging the side of their ambivalence I had been unknowingly carrying for them in a way they had just previously been resisting.

The goal of helping patients own and tolerate both sides of their ambivalent feelings about marijuana (or any other drug or behavior) becomes more achievable if clinicians normalize ambivalence, and even praise a patient's being open and honest about it. Everyone experiences ambivalence all the time. Clinicians can demonstrate this by acknowledging they would like to be relaxing at home instead of working, but they know work is more important at the moment. Ambivalence is merely having opposite feelings about something, like wanting to eat a lot of ice cream but not wanting to consume that many calories. Ambivalence is a normal part of having many, many feelings active at the same time. It is a sign of psychological growth to be willing to acknowledge ambivalent feelings and not to be ashamed of them. Ambivalence is an

opportunity to make a choice at the same time that it complicates choosing – because in choosing something is always lost.

2 Increasing Cognitive Dissonance

One of the most powerful interventions clinicians can make is to admit their confusion in the face of discrepancies between a patient's behavior and their values. I have often encountered substance abusers who will not use aspirin for a fever because they do not like taking chemicals into their body. While my first impulse may be to laugh at the ridiculousness of their inconsistency or to sling a sarcastic remark that I might toward a friend with such behavior, a much more powerful stance is to admit that I do not understand. My goal is to get the patient to see the inconsistency and this is accomplished more by asking them to explain their behavior than by anything I might say about it. The message I want to give is "Teach me; help me understand how you can value keeping your body clean from chemicals like aspirin while freely smoking marijuana (or drinking alcohol, using opiates, amphetamine, etc.)." This is really a fascinating question. It gets right to the core of how people can self-justify self-destructive behavior. There is, of course, no fully satisfactory answer; and so I continue to not understand when patients try to explain the inexplicable.

The goal here is to increase the cognitive dissonance being experienced by patients. People feel discomfort when they become aware of holding two or more contradictory beliefs, ideas, or values.[12,13] Cognitive dissonance occurs when new facts that cannot be denied clash with established beliefs or values. People search for ways to resolve the contradiction in order to reduce their discomfort, sometimes by finding ways to ignore or cast the facts into doubt, but sometimes by changing their beliefs and values. We see people today refusing to accept scientific facts regarding climate change in order to hold onto their current energy behaviors. The comedian Robin Williams said of his relapse into alcoholism that he violated his values faster than he could lower them. And, sometimes they change their behavior on the basis of learning new facts in order to maintain their values.

The primacy of effective engagement is clear when guiding patients into increased cognitive dissonance. When given a nonjudgmental and supportive environment that accepts ambivalence as normal, patients are better able to tolerate the discomfort of seeing the contradictions between their values and their behavior without quickly finding ways to deny or justify the discrepancies. When clinicians can tolerate and explore the contradictions with genuine curiosity, patients can be heartened to sustain their self-exploration.

3 Avoiding Argument

Whatever arguments exist need to be seen as lying solely within patients' internal conflicts and ambivalence. Clinicians need to avoid being enlisted as combatants despite many substance abusers' uncanny ability to provoke defensive responses by others. Arguing a point with patients appropriates one pole of their ambivalence, making it "not them." Arguing also works against patients feeling that their experience is being respected. Perhaps most importantly, arguing that patients should accept your point of view is guaranteed to strengthen their defenses against you, and against self-exploration. No one wants to feel attacked for his or her beliefs. Resisting external pressure to deny

their feelings or beliefs becomes a matter of self-esteem and pride. Clinicians have begun to lose any opportunity for a cooperative approach to solving patients' problems when they enter into an argument, no matter how right a clinician may be. And no matter how foolish the patient is being. The much more powerful, and respectful, approach is to admit confusion and an inability to understand a patient's perspective. Ask for help. Ask for patients to explain what they mean and how it makes sense to them. This is the judo expert's practice of "going with the resistance" rather than opposing it with greater force. The latter tactic gets nowhere, while the former may get deeper into a patient's inner world, and even deeper into a collaborative relationship.

Avoiding arguments does not mean agreeing with patients' false beliefs or misinterpretations of facts. Clinicians need only say they do not see things in the same way, but rather than put energy into explaining your perspective (unless asked by someone with an open mind) you should express interest in understanding why your patients hold the beliefs they do. I am often surprised by the interesting answers patients give, and I often begin understanding why they might see things the way they do. But this does not mean I agree with them. By tolerating different perspectives within the relationship, clinicians model how an individual might tolerate different, even contradictory, points of view within themselves – cognitive dissonance.

4 Reinterpreting Resistance

Resistance is an important signal that a collaborative effort between patient and clinician is in jeopardy and must be responded to in a way that does not intensify defensiveness. Miller describes four categories of resistance, from patients' *interrupting*, hostile *arguing* and discounting, *denying* and blaming, and *ignoring* (often by deflection). I assume that the average clinician dislikes being challenged hostilely, interrupted, or ignored as much as I do. In a purely social context I feel disrespected when treated with such loutish behavior. But clinical practice is not a social setting and emotional reactions are not the best guides for how to respond. Clinicians need to reinterpret patients' resistance as a sign of their feeling threatened, and their seeing the clinician as a potential predator. Given their experience of feeling threatened, although based on a misperception of the clinician's intentions, they should be seen as protecting themselves as fiercely as any self-respecting and vital person would when feeling under attack. If the clinician does not want to lose any chance of engaging resistant patients, a nonjudgmental, nonargumentative empathic response to resistance is necessary. While many clinicians cringe at the adage to "Go with the resistance," this should be seen as a too facile reframe of the important psychoanalytic principle of "honoring the defense before interpreting the underlying impulse." Both phrases contain the wisdom and art of timing that is so important for maintaining engagement while also directing patients toward their ambivalence and cognitive dissonance.

A variety of responses to resistance are available. Sometimes merely repeating a patient's denial or blaming is enough to communicate that you are listening. Sometimes amplifying a patient's objections communicates what they really meant to say, or paradoxically can flip them to the other side of their ambivalence to clarify that they do not feel quite as strongly as the clinician described. Or you could acknowledge what the patient has said but then wonder about contrary things they have previously said. Sometimes shifting the focus to a more neutral topic is necessary to defuse a moment of resistance. Behavior that a patient denies is problematic can be reframed

as their attempt to solve a broader problem (e.g., "Drinking seems like the only way you can cope with your marriage falling apart," which can serve as a prelude to exploring how drinking also paradoxically further jeopardizes the marriage). The goal is always to keep the conversation going, often circling around a patient's primary problem until it is seen from multiple directions while always searching for any signs of ambivalence and working to enhance cognitive dissonance.

5 Optimism that Patients Can Change

The perspective introduced in the previous chapter of being "powerless" to *make* a person change by dint of our own will power sets the stage for clinicians to understand that the fundamental task of motivational interviewing is to enlist patients into the process of change. Ultimately it is only the patient who is responsible for choosing and carrying out personal change. Belief in the ability to apply one's own efforts to effecting change is what is meant by the term "self-efficacy." A clinician's task is to hold firm to the belief that patients have enough self-efficacy to change if they find the motivation within themselves to do the necessary work.

MI puts more effort into helping patients "recognize how life might be better and choose ways to make it so"[14] than it puts into identifying the problem and trying to convince patients they need transformational change. This does not mean blindly cheering patients on, as though our motivation can somehow be transmitted to them. Rather, it means holding the fundamental belief as a matter of fact that, if patients find the motivation, they can change behavior. We help them find this motivation within by engaging them in an honest discussion of concerns they have about themselves. Motivational interviewing entices more than it persuades or tells (i.e., lectures). When it works well, motivational interviewing facilitates patient generated, directed, and sustained change. When it only partially works, motivational interviewing provides a positive experience with a clinician and plants valuable seeds of change that wait for the proper circumstances to germinate.

Concluding Comments on Motivational Interviewing

The practice of motivational interviewing is an art. While it can be codified for teaching purposes, its practice requires a continuously spontaneous creativity on a clinician's part to respond to each unique individual's momentary state of mind. Understanding the principles of motivational interviewing is easier than practicing them, though some practitioners look like naturals from the outset. Perhaps differences in the ease of integrating these principles into daily practice lie in William Miller's assertion that "Motivational interviewing is a way of being with a … [patient], not just a set of techniques …"[15] Practicing the art well is easier for those who have integrated the perspectives that guide Al-Anon. While it may initially seem extreme to say that practicing motivational interviewing well requires an inner purification process, I do think that achieving and sustaining humility, nonjudgmental regard for others, and a realistic understanding of the limits of our power to change others has a profound impact on the ability to practice motivational interviewing well.

I hope I have given a clear and accurate overview of motivational interviewing in this brief chapter and refer those interested in more detail to the sources referenced. Readers who would like to see what motivational interviewing looks like in its moment to

moment practice can view an excellent 15 minute demonstration at the website: www.youtube.com/watch?v=FBDIl0ftIdc

The following chapter describes treatment for adolescent Cannabis Use Disorder (CUD), including how I integrate the science of marijuana reviewed in Section 1 into a motivational interviewing framework.

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Chapter

13 Treatment of Regular Heavy Marijuana Users

Every clinician encounters people whose lives are compromised by marijuana, whether recognized by the individual or not. Forty-eight percent (48%) of American adults acknowledge lifetime marijuana use, with 12% of the general public having used marijuana during the past year. Use rates among younger age groups are highest, with 27% of those under 30 acknowledging use in the last year.[1]

However, past, or even present, marijuana use does not automatically denote problematic use. While use of any drug, whether by prescription, over the counter, recreational, or illicit, always entails some degree of health risk, the majority of marijuana users manage this risk responsibly. The number of "current users" in the U.S. (i.e., past month) in 2007 was 14.5 million (5.8% of the population). This number rose to 18.9 million in 2012 (7.3%).[2] Monthly use is not heavy use, although it is frequent enough to have significant adverse consequences in a few selected populations, e.g., bipolar disorder, schizophrenia, addictive disease, or for those on probation, particularly in countries and the U.S. states where recreational marijuana remains illegal.

Regular marijuana use, defined as daily or almost daily use of marijuana (20 or more days in the past month) existed for 7.6 million Americans in 2012, up from 5.1 million in 2007.[3] Perhaps most worrisome, due to the increased vulnerability of the developing brain, 6.5% of high school seniors reported smoking marijuana daily in 2012, up from 5.1% five years previously.[4]

Attention needs to be paid to distinguishing mere use of marijuana from harmful involvement with the drug, whether this involves full addiction or not. People do not have a drug problem unless problems can be identified that are caused, or exacerbated, by their drug use. Familiarity with the diagnostic criteria for CUD and the often subtle symptoms of withdrawal helps make this distinction. The level of training possessed by clinicians regarding these objective criteria varies widely and affects their conclusions. At

the same time, the level of professionals' experience with marijuana abusers also affects their sensitivity to the rationalizations, preoccupation, alterations in lifestyle, and psychological/emotional impacts associated with excessive marijuana use. The following description of treatment assumes that a proper evaluation has been conducted and little doubt remains that the individual seeking help would significantly benefit from reducing, or abstaining from, their use of marijuana.

While adult heavy users usually establish therapeutic contact themselves (often in response to a partner's pressure or for reasons seemingly unrelated to marijuana use), the parents of heavy adolescent users are more likely to make the initial contact. I usually ask whether their child has expressed interest in speaking with someone. When their child is interested, I typically meet with him or her first and with the parents after a therapeutic alliance has been initiated with the adolescent. If the parents are unsure whether a problem exists or when their child refuses to participate, I initiate evaluation and treatment, if necessary, with the parents themselves. The goals are to evaluate their understanding of marijuana, to provide needed information, to assess their own relationship to drugs and alcohol, and to guide them toward healthier strategies for dealing with a potentially active addict. In most cases this involves making a referral to Al-Anon meetings that specifically focus on parents of addicts. In cases where the adolescent is unwilling to enter any form of evaluation or treatment, I need to counsel parents on how to use a contracting process to set boundaries for their home.[5] Contracting involves a written description of objectively measurable responsibilities (e.g., keeping room clean, attending school, maintaining clean drug tests), clearly defined consequences (e.g., loss of specified privileges, formal evaluation by addiction specialist), and support provided by parents (e.g., parental abstention from all psychoactive substances themselves, access to a therapist), signed by all parties. Obstacles encountered in the negotiation of such a contract provide clinicians with reams of useful information about a family's dynamics.

At this point there are two directions any discussion of treatment can take. The traditional direction found in today's medical literature is to review outcomes of, and comparisons between, various standardized treatment modalities. A host of "alphabet" therapies have been developed and manualized. Producing a written manual to structure and guide a treatment program increases the likelihood that results will be similar for all clinicians. It also allows for specific forms of therapy to be researched. While standardized treatment protocols facilitate research, they fail to utilize clinicians' experience and creativity. Reliable evidence of benefit is gathered, but the conversation becomes one of "treatment technologies" rather than the "art of healing."

SAMHSA tested five of the most prominent short-term outpatient intervention models for treating adolescents with CUD in a project called the Cannabis Youth Treatment (CYT) Study.[6,7] The five forms of treatment offered to 600 cannabis users (aged 15–16) in several combinations and intensities were Motivational Enhancement Therapy, Cognitive Behavioral Treatment offered in 5 or 12 session doses, Adolescent Community Reinforcement Approach, Multidimensional Family Therapy, and Family Support Network. Clinical outcomes were similar across all five modalities. There were no statistically significant differences in pre-post treatment improvements over 12 months as measured by days of abstinence and the percent of adolescents in recovery (no use or abuse/dependence problems and living in the community). The CYT Study showed that, while interventions were often initially effective, half of the adolescents experienced relapse one or more times after discharge. Two thirds still reported

substance use or related problems at 12-month follow-up, which means that one third no longer experience problematic use. The study's authors concluded that cannabis diagnoses are best understood as chronic conditions requiring greater focus on long-term monitoring and care.

The state of the art of treatment research has produced evidence only that a variety of treatment programs provide measurable help to adolescent marijuana users, but no one form of treatment is better than the others. A problem inadvertently created by "evidence-based treatment", when applied to psychotherapy and counseling, is that, in order for research to provide reliable and reproducible results, variables have to be eliminated as much as possible, including the clinicians' skill, experience, and creativity in individualizing treatment. Unfortunately, this is like measuring people's satisfaction with different meals after first breaking each down into its nutritional elements in order to eliminate the influence different chefs contribute with their cooking styles.

I am not disparaging either manualized treatment programs or the research done by the CYT Study. A particularly valuable manual for clinicians treating adults is SAMHSA's public domain "Brief Counseling for Marijuana Dependence" freely available on the Internet.[8] I only mean to put manualized treatment approaches into a different perspective. They are tools with proven effectiveness but not the whole of what treatment has to offer. They are perhaps the best approach to use with younger, less experienced staff. The role of the fully trained and experienced clinician needs to be put back into the equation, although this immediately makes treatment research almost impossible.

The second direction a discussion of treatment can take is more personal and descriptive. I will offer a distillation of the approach that has worked best for myself, recognizing that every clinician has her or his own unique personality with which to connect with patients. Following is the way I use my own idiosyncratic skills and weaknesses to help people suffering from harmful involvement with the marijuana they love.

My approach to a discussion with heavy users about marijuana is guided by taking care not to add fuel to their defenses. The initial goal is to engage patients – to develop mutual ground for discussion. This essential alliance requires a truly nonjudgmental stance that embodies genuine curiosity. Most heavy marijuana users are willing, even eager, to discuss their use if their defenses are initially honored rather than immediately challenged, no matter how gently. Motivational interviewing requires clinicians to engage in active dialogue with patients – what often looks like "mere" conversation. When engagement is achieved, even single session interventions have demonstrated significant declines in marijuana use at three-month follow-up in both adults and adolescents.[9,10]

I usually preface any questions by saying I have spoken to hundreds of people about how they experience pot and I know it is not the same for everyone. This both establishes some authority and invites patients to describe their own unique experience. Typical questions I then ask to open a discussion are, "What do you enjoy the most about marijuana?", "How is being high different from being drunk?", or "What is the most valuable thing marijuana has taught you?" When patients give one dimensional or vague answers (e.g., "Makes me feel good"), I drill in deeper. There are many different ways marijuana helps people "feel good" because there are very many ways people feel bad. I try to communicate my genuine curiosity about the granular details of each individual's experience. I encourage them to teach me, which establishes my willingness to listen.

Whatever expertise I might have, the patient alone is an expert on his or her own experience. I want them to know that I need their collaboration to have a clear idea of what they like about marijuana – what is added to, taken away from, or changed in their experience.

After patients begin helping me understand what they like about marijuana, I can initiate a three-step process. First, I store away the information given me about what they like changing in their life by using marijuana. For example, if they most enjoy the relaxation from marijuana, I know that I will have to help them deal with their anxiety/stress/tension if they decide to stop using. If they enjoy the virtual novelty stimulated by marijuana, I will eventually have to deal with their sense of boredom and lack of meaningful activities without it.

After patients can no longer think of additional ways marijuana affects them, I ask about several specific experiences patients may not have spontaneously brought up, such as lessened anxiety, increased appetite, enhanced sensory pleasures and a sense of freshness/novelty. It is best not to initiate this line of inquiry until assured that I am not simply putting words in a patient's mouth with my prompts, but rather supplying words for their experience that flesh out a wider range of marijuana's impact. This also further establishes my bona fides as a marijuana expert. For example, when explaining what I mean by "novelty," I often describe the experience of noticing small rainbows on the exact same place on every soap bubble, a perception they had stopped noticing after preschool until marijuana lowered the bar for sensing novelty. Another example I use is that pot makes a trip down the hall to the bathroom an adventure. Most marijuana users enjoy these examples and often enthusiastically begin offering some of their own. The word "novelty" provides many with a new framework for thinking about what they like about marijuana. In those cases when I ask about a typical experience such as novelty that draws a blank for a patient, I use this as an example of how marijuana affects different people differently.

The second step is to ask what a patient knows about how marijuana produces the experiences they most value. People generally know that THC is the active ingredient and an increasing number know about marijuana receptors, but few have any deeper understanding. Most are interested to learn that cannabinoid receptors are the most numerous receptors in the brain; and the reason they exist is because the brain produces its own marijuana-like chemicals! To be more accurate, though, I say we should see the cannabis plant as producing brain-like chemicals. THC, and all the other cannabinoid molecules in marijuana, are powerful only because they resemble our brain's natural chemistry. THC *mimics* our brain chemistry and thereby increases the activity of our natural cannabinoid system to a level never experienced normally. I drop the fascinating question of what the function is of our brain's cannabinoid system as an anchor to be returned to later. The more genuinely fascinated *I* am by this question, the more likely I can pique someone else's curiosity later.

Then I focus on the experiences each patient most values – relaxation/reduced anxiety, novelty/pleasure, or sensory enhancement/munchies – to introduce a deeper understanding of the endocannabinoid system. Most heavy smokers, though not all, are fascinated by learning more about the drug they are in thrall with. In the process I will be increasingly moving the focus from the plant to their brain.

I may explain how the brain's natural cannabinoid system is constantly regulating our sensitivity to novelty to fit different tasks. This permits me to introduce the

concept of cannabinoid tone. When hunting we want to notice the subtlest new stimulus; but when concentrating on a single task we might want to filter out distractions, no matter how novel they are. The cloud of THC that marijuana generates lowers the bar for our brain's producing the sense of novelty in reaction to stimuli. This freshens our perceptions in a very enjoyable manner. At this point, many patients are fully enthusiastic about the wonders marijuana brings into their life by heavily stimulating our natural cannabinoid receptors. Once engaged, many describe unique ways marijuana changes their subjective experience. I let them teach me and ask for more details, sometimes noting the portion of the brain involved with different experiences – amygdala, hippocampus, etc. This helps people begin more richly verbalizing what have previously been only vague impressions.

Another example that is easily understood is the modulation of short-term memory by our endocannabinoid tone. Increasing tone shortens short-term memory and decreasing tone lengthens it. Life presents varied tasks for which different amounts of short-term memory are most useful. Attempting to remember a phone number until it can be recorded may benefit from our being able to hold the number in memory for many seconds. However, holding onto the memory of what happened 15 seconds ago is likely to make a basketball player less effective. Still focusing on what happened at the other end of the court could make a player lose half a step to an opponent and that is all that is needed to be beaten. Most people can understand the value of their brain's ability to modulate the parameters of short-term memory, and most heavy marijuana users have experienced truncated short-term memory when intoxicated. THC can lead a person to forget the subject of a sentence by the time they get to the predicate. My goal here is to flesh out the idea that impacts on specific parts of the brain underlie the psychoactive properties of marijuana and that this involves overloading the normal balance.

I can now also begin activating a patient's ambivalence, the third step I have been setting up, by introducing the phenomenon of receptor downregulation. Simply saying, "Marijuana eventually dulls the mind," is too vague and clearly designed to be threatening. I need to give a visual, concrete picture of what happens when the cloud of THC dissipates and fewer than normal CB1 receptors remain for the normal level of endocannabinoids to activate. Describing the sucking of receptors into the cell's interior to reduce excessive stimulation fascinates some people. The result of downregulation and resultant reduced cannabinoid tone in the amygdala is that the bar for experiencing novelty rises above normal, and everything becomes more boring – unless marijuana is reused. The calming effect of marijuana is also reversed when there are too few receptors to respond to our normal level of cannabinoid chemistry, resulting in increased anxiety or irritability (the opposite of "chilling"). A roller coaster develops in which sensations are freshened when using marijuana, then boredom and anxiety/irritability/restlessness return when the cloud of marijuana recedes. Boredom, especially when tinged with restlessness and irritability, is difficult for anyone to tolerate, not when a remedy is immediately at hand. Receptor downregulation is the inevitable fly in the ointment.[11] Downregulation causes the uncomfortable state of cannabinoid deficiency.

Once the concept of cannabinoid deficiency, on the basis of downregulated CB1 receptors, has been established, it is safer to begin approaching the question of dependence/addiction. At first, I avoid the two words "dependence" and "addiction." These two words are much more difficult for people to identify with than "cannabinoid deficiency." They are anathema to many who deny the existence of marijuana addiction and view any

mention of addiction as "*Reefer Madness*" propaganda and lies. I do not jump into these weeds initially in order not to jeopardize whatever fragile relationship has developed up to this point. Heavy marijuana users are often comfortable acknowledging the discomfort of being unable to use their drug of choice when this is labeled a "deficiency" of the cannabinoid stimulation they enjoy. They know this feels bad. My goal here is to establish that the bad feelings are not simply due to someone's interfering with their right to smoke pot. Their discomfort is also the result of a brain that has been modified by their regular marijuana use and is left out of balance when they are unable to be high, i.e., a cannabinoid deficiency state. I can empathize with how this feels.

I can approach the question of addiction/dependence safely only after exploring whether a patient has experienced cannabinoid deficiency when their use is interrupted (boredom, lack of motivation, increased anxiety, insomnia, restlessness, irritability). At this point I may ask directly if a patient believes marijuana is addictive, or if they themselves have become dependent to any degree?

A surprising number of patients readily acknowledge addiction, though many still dismiss being addicted as any more important than coffee addiction. When there is openness to discussing the addictive nature of marijuana, I often mention the work of Alan Budney showing that the intensity of withdrawal most closely resembles that of tobacco.[12] Not a life and death matter. On the other hand, as with tobacco, relapse often occurs largely to quell the nagging symptoms of withdrawal. (Note how long it took me to use the word "withdrawal" for the first time.)

At its core, marijuana dependence resembles all other drug dependencies. In Hamlet's words, "As if increase of appetite had grown by what it fed on . . . " This is the essential nature of addiction. "Wanting" increases and can even be more dominant than "liking".

However, I strongly caution clinicians that it is paramount to explore whether they themselves believe marijuana is addictive before discussing its dependence with patients. If a clinician does not hold this belief, or does not understand the four lines of evidence substantiating the existence of marijuana dependence (increased dopamine in the reward center, animal studies of precipitated withdrawal, human clinical reports, and epidemiological surveys), he or she is not in the best position to help someone find recovery. In fact, no clinician should attempt to treat a marijuana user without first exploring with rigorous honesty their own personal relationship with marijuana. This requirement is of the highest ethical importance.

Several common themes run through patients' denials that marijuana is addictive or can cause problems, almost as if they are talking to one another. This is because they are part of a tight community whose members *are*, at least indirectly, talking to each other through the ethos and mores binding stoner culture together, aided by the Internet (see Erowid.org). It helps to be armed ahead of time with responses to the typical patterns of denial outlined in the previous chapter in order to advance to the next step in treatment – evoking ambivalence and cognitive dissonance.

The goal of this next stage, again, is not to prove patients wrong, but rather to create cognitive dissonance and stimulate dialogue. The primary avenue for creating cognitive dissonance is confronting patients with new information that is incompatible with their existing beliefs. I share scientific facts, often with a summary of the research establishing them, in order to make avoidance more difficult and to explain why I am unable to reconcile the science with patient's experiences. By my failing to understand how to reconcile a patient's contentions with incompatible facts and perspectives, I create an opportunity

for a patient's ambivalence to rise into the discussion. Together we wrestle with the conundrum of their beliefs being challenged by research discoveries. As ambivalence develops, the readiness to change increases.

I have three laboratory experiments that are my favorites to describe in some detail at this point. First, I like to describe Susan Tapert's go/no-go research protocol.[13]

To review briefly, when regular marijuana users and non-users are asked to respond as quickly as possible to visual stimuli on a computer screen, but to refrain from responding to a few specific stimuli, both groups perform equally well. Regular marijuana users take this as confirmation that no harm is occurring. Functional MRI results, however, differ. The brains of regular users activate all the areas seen activated in non-users plus additional areas. Does this mean that marijuana enables people to use more of their brains, or does it make brains less efficient and need to recruit additional areas to compensate? I do not need to answer this question, but merely to pose it. The bottom line is that regular marijuana use alters brain activity.

Second, details of the Iowa Gambling Task are usually inherently interesting to people.[14] By explaining how regular marijuana users tend to overvalue card decks with large gains, but also large losses that lead to smaller net rewards, I can introduce several relevant implications. For example, being "chill" is aided by not reacting as much as most people to negative events. "Don't worry; be happy." "Don't sweat the small stuff, and almost everything is small stuff." Unfortunately, overlooking negative results interferes with learning from our mistakes. It may seem great not to fear risk, but fear is the emotion that teaches us how to avoid taking the same bad risks over and over. The bottom line is that marijuana alters our strategies for assessing risk. Using marijuana is a choice everyone is free to make, but it is usually best to be conscious of the consequences of our choices.

The third piece of research I often describe in some detail is Staci Gruber's Masked Faces Protocol.[15] The concept of subliminal stimuli used in this protocol fascinates most people. I combine this with the fact that activity is seen in the emotion generating amygdala in response to subliminal exposure to a fearful face *without any conscious awareness of the stimulus*. I marvel at having an fMRI photograph of the unconscious! Except, there is no response to subtle emotional cues in chronic marijuana users. Again, this is part of being "chill." But it directly challenges many people's experience of feeling more sensitive to their environment, including the emotional state of a partner, when stoned. On the other hand, I had one really sharp patient challenge me by pointing out that the subjects in this research were not high at the time of the experiment. Maybe, he said, they are normally less sensitive to emotional cues, and using marijuana increases their sensitivity – a good thing. His logic was good, though the most likely cause is still cannabinoid deficiency due to downregulation from heavy marijuana use. His observations illustrate just how difficult research can be. Perhaps the experiment needs to be repeated after giving heavy users a dose of marijuana. And, to be more complete, some non-users need to be tested in the Masked Faces Protocol to record a baseline, then be asked to use marijuana heavily enough to cause receptor downregulation (an ethically unacceptable request) to see if they become less sensitive to the subliminal stimulus. Even then, it may be that they differ from regular marijuana users because they did not have the genetic or psychological makeup to become regular marijuana users spontaneously.

I went to some length in the preceding paragraph not only to illustrate how difficult good research can be but also to depict how resistant some people will be to having their cherished beliefs challenged. It is important to remember how resistant we all are to

having our most firmly held beliefs questioned. There is nothing unique about heavy marijuana users in this regard. And, like everyone else, they are unlikely to react well to a frontal assault on the defenses erected to protect what they honestly believe is true. Unfortunately, marijuana can become such a central organizing principle in a person's life that admitting any ambivalence feels like a defeat. Not everyone is open to being helped, despite our best efforts.

One clever, though unconscious, way people have of avoiding their ambivalence is to disown one pole of their divided thinking. When we cannot tolerate being torn by incompatible pressures, we can project one of them out into someone else. For example, a young adult who is failing to launch may harbor both the belief that maybe they should get a responsible job and that a career would rob them of a childhood they have not yet completed. By projecting the belief that they should get a job onto a parent, they can now release the child-like part of themselves to battle their parent rather than do the difficult work of resolving an internal dilemma. In the same way, the most devoted marijuana users end up fighting people who want them to stop rather than owning any ambivalence they might have about their use.

It is of paramount importance not to become identified with *either* pole of a patient's ambivalence. I realize I have again made this mistake whenever I get into a struggle with a patient. Then I need to step back out of the conflict. It is not me who is applying pressure to get them to stop using. It is the facts – the science – that gets stuck in their craw. I am just the messenger. My success cannot be measured by whether I get any particular patient to stop using marijuana. If they stop, it is they themselves who decide to stop. I do not want them to come to this decision in response to the force of my personality or my desire for them to stop. This never lasts. I want them to come to this decision on the basis of their own motivation, guided by facts they can no longer deny. My job is to stay in respectful relationship with them long enough for us to explore their ambivalence evoked by the facts science has established. I do not have to challenge their beliefs. I merely need to not understand how a distorted belief can be held onto in the face of contrary facts. I need to keep bringing up the science that is incompatible with their beliefs and work with them toward understanding why this incompatibility exists. Many a time I have had to sit back in the face of a patient's insistence that they are not addicted and wonder aloud what I am supposed to do with what they have told me about being anxious, irritable, and having insomnia when they cannot use marijuana. I hope that the relationship is solid enough that I can keep them trying to explain away the cognitive dissonance created by the science. The conversation is not over as long as they do not tell me to throw science on the trash heap of conspiracy theory and propaganda.

Treatment depends on developing a non-confrontational empathic relationship, beginning with eliciting the patient's experience with marijuana. By nonjudgmentally respecting a person's reasons for using marijuana – their perceived benefits – a treatment alliance can develop, based on the clinician's communicating an empathic connection to the patient's experience. This therapeutic alliance provides the context for presenting factual information about marijuana and the brain that is directly related to patients' experiences, resulting in cognitive dissonance. The principles of motivational interviewing respect patients' ambivalence and encourage them to wrestle, together with the clinician, with uncomfortable new information. Clinicians need detailed understanding of the science of marijuana and the brain's endogenous cannabinoid system in order to help patients see through their rationalizations. In addition, clinicians must create a safe arena for discourse by a deeply nonjudgmental attitude. Genuine curiosity about

patients' subjective experiences is the most effective avenue for successful engagement. No manualized treatment protocol can communicate empathy without the human connection offered by a skilled clinician.

The human element, whether available from a clinician or peers, is especially critical to the next stage of change – harm reduction or abstinence. After I have provided enough information about harms caused by heavy marijuana use to produce cognitive dissonance, I pose the question, "What if marijuana is causing more problems than you have realized – more than it is solving? *If* that is true, it would be a shame never to see this." The question is hard to argue with since it is hypothetical. People may remain convinced that there is no harm from their marijuana use and yet it is still true that it would be unfortunate if there *were* harm that they never realized. There is really no good way for a marijuana user to confirm their belief pot is all good short of reducing or eliminating its use. I certainly have no way of producing evidence outside of their willingness to show me, through a period of abstinence, that marijuana is producing more good than harm. But, of course there will be a six-week washout period during which they are likely to feel worse if any withdrawal symptoms appear. Sometimes there are no withdrawal symptoms. This is good because it means that the alteration to the brain is less than had been predicted. Other times there are withdrawal symptoms but they are denied. It is more important for the patient than for the clinician to know withdrawal symptoms exist. We are on a scientific exploration together – a single case study. It does not mean that patients cannot return to using marijuana at any point if they wish. They will always have the freedom and the right to make this choice. But they will never be able to return to using again without knowing they are choosing addiction. I have no trouble wishing people well no matter how they decide. When there are obviously uncomfortable withdrawal symptoms, the abstinence trial can greatly intensify the discomfort of a patient's cognitive dissonance and the clinician's empathy for this discomfort is often critical support for patients. They need to continue tolerating withdrawal if they hope to progress to real change. Praise for their willingness to grind through the early stages of abstinence and reminders of the potential benefits of sticking with it can make all the difference.

There are cases when people are unable to reduce their marijuana consumption without help. As a physician, I am also aware that Kevin Gray reported the supplement N-acetylcysteine (NAC) at 1200 mg twice a day showed more than double the odds of having negative urines in adolescents (ages 15–21), compared with placebo, detectable within a week of treatment initiation, although a later study of adults (ages 18–50) showed no benefit of NAC.[16,17] He is currently conducting another adolescent trial to shed more light on NAC's different impacts on adolescents and adults.[18] It is important to understand that these results were obtained with youth who were in an active treatment program and I am unaware of any replication of these results. It is unknown whether simply taking the supplement would have the same impact for those not in treatment. At the same time, offering the suggestion to use NAC provides hope, and a patient's willingness to try it acknowledges the need for help.

A different medication, gabapentin 1200 mg daily in divided doses, has been shown to reduce withdrawal symptoms, including craving and disturbances in mood and sleep. Perhaps more important for people in treatment, gabapentin produces greater overall improvement in executive functioning compared to placebo.[19] Again,

these results were documented in people participating in a structured treatment program and may not generalize to people not involved in treatment. The value of more quickly regaining one's full executive functions during treatment is that recovery depends upon what is called "shifting set." Just as a person taking the Wisconsin Card Sort Test has to switch from sorting cards by color to sorting by shape, for example, people entering recovery need to reinterpret the effect of their marijuana use from being the solution to being the problem. Rather than believing that marijuana is the balm that helps them tolerate their life's problems, they need to see the extent to which marijuana might be the irritant that intensifies their difficulties as well as chilling out its discomfort. Intact executive functions and mental flexibility are necessary for making this radical change in perspective.

Building an Adolescent Treatment System

Most of my professional career has been conducted in private practice, which may lead to the misimpression that the treatment process outlined above is applicable only to one-on-one therapy. Nothing could be further from the truth. Structured treatment programs heavily relying on peer groups are an important, and often preferred, treatment modality for adolescent CUD. Treatment in program setting can be guided by the same processes of empathic engagement, motivational interviewing, stages of change, and reliance on a scientific understanding of marijuana and the brain.

With legalization of recreational marijuana in California, whose population of over 39 million is larger than Canada, an estimated $500 million will eventually become available for education, prevention, early intervention, and treatment of adolescent substance abuse. This windfall of new tax revenue offers an opportunity to build a comprehensive treatment system for the state's youth. There has not been an opportunity like this since the end of alcohol prohibition in late 1933. Unfortunately, taxation of alcohol was kept too low to fund treatment of the damage it has subsequently done and the exigencies of the Great Depression caused revenue to be directed toward the general fund. Enough marijuana advocates in California acknowledged what science has discovered about the potential for harm among adolescent users that writers of the recent Control, Regulate and Tax Adult Use of Marijuana Act (AUMA) specifically directed 60% of tax revenue above administrative costs and carve outs toward youth, to assure substantial treatment services for the population most vulnerable to marijuana. While it can be debated whether it is responsible to legalize marijuana, there can be no debate that committing the marijuana industry to pay for damage it produces makes sense. All business should be held to such a standard. There would likely be little adolescent use of marijuana if no adults grew, distributed, and used it. Therefore, adult users are responsible for creating the attractive nuisance marijuana presents to youth.

My argument during the writing of AUMA was that, while youth already had nearly unlimited access to marijuana, they had very limited access to treatment. Only the wealthy, or those able to get a second home mortgage, were able to send their addicted children to expensive wilderness programs and therapeutic boarding schools. With the anticipated availability of a conservatively estimated half a billion dollars, attention is now turning to developing an effective treatment system for youth. Unfortunately, the U.S. still does not have a universal healthcare system like most other industrialized countries. We still labor under the burden of permitting healthcare to lie within the legitimate purview of private

enterprise. Competition and marketing for consumers' and government tax dollars fragments the "system" of care to the detriment of all but large medical, insurance, and pharmaceutical corporations. In an effort to assure that marijuana tax revenue dedicated to youth is used effectively, the California Society of Addiction Medicine (CSAM) has advanced the following framework for a system of care for adolescent substance abuse.[20]

To begin, standards for youth treatment programs need to be developed and enforced in order to assure that all funded programs fit into a continuum of care. Without quality standards, funds will be distributed to grantees with the best marketing skills and care will remain fragmented and of uneven quality.

The workplace for adolescents is school. The goal should be to keep as many adolescents in school as possible in order to protect their education, future employability, and independence. The most effective way to support adolescents is to bring the same kinds of services into schools that are offered by Employee Assistance Programs (EAPs). Student Assistance Programs (SAPs) provide effective drug education, prevention, early intervention, and referral to treatment when necessary.[21,22] The best SAPs offer three levels of prevention outlined by the Institute of Medicine.[23] *Universal* prevention is directed to the entire school population. It is the least expensive and reaches the widest audience. *Selected* prevention targets high-risk groups, e.g., middle schoolers transitioning into high school or students who self-identify as coming from families with addiction. *Indicated* prevention focuses on individuals beginning to manifest problematic behavior. For example, a student caught smoking pot on the school grounds could be assigned a number of introductory sessions with the SAP counselor rather than being suspended (which only interrupts their education, interferes with parental work schedules, and often provides a few days without supervision). Many insipient problems can be remediated at the school level before they worsen enough to require formal treatment. SAPs should have the capacity to evaluate potential learning disabilities, which occur at a higher frequency in substance abusers. SAPs are also in a perfect position to work toward creating changes in the social mores of the school environment in order to destigmatize seeking help and create a recovery sensitive culture to support students in treatment. It is only when a diagnosis of SUD is likely that SAPs refer students to the next higher level of care for formal evaluation and possible treatment.

When a diagnosis of SUD is established and treatment is required, it should be provided separate from adults for several important reasons. Safety is a primary concern. People in early recovery are vulnerable. Bonds with old friends who are still using are being loosened, which leave many adrift without a tribe. The need to belong to a community is strong and yet the ability to maintain appropriate personal boundaries may not be well developed yet. It is hard to avoid forming intense attachments, often highly sexualized, that interfere with doing the hard work of recovery from addiction. For these same reasons, gender specific groups should also be available to minimize the distractions of adolescent sexual interests.

While adult treatment programs usually offer some degree of family treatment, this needs to be a critical focus for adolescents. Most are still deeply dependent on family. Parental consent needs to be obtained for treatment. Transportation to treatment appointments needs to be provided. Support for the whole family's recovery, including siblings, is one of the strongest influences treatment programs can provide. And above all else, issues of family trauma, abuse, neglect, and parental alcohol or other drug use need to be addressed.

One size does *not* fit all adolescents. A 13-year-old is at a very different stage of development than a 17-year-old. The treatment goals for each are the same: recovery from substance abuse and getting the process of maturation back on track. But age appropriate messages for the youngest adolescents may seem childish to older adolescents, while messages for the older adolescents may be inappropriate for younger ones. The bottom line is that treatment of adolescents often requires a much greater level of sophistication and staff training than needed for treating adults.

Ideally, there should be one or more adolescent outpatient clinics in each county, depending on the youth population base. These clinics should provide psychological and physical evaluations and intensive outpatient programs as well as ongoing long-term outpatient care. Treatment needs to be conceptualized as ongoing support throughout adolescence and not as a one-time event. Relapse is common and adolescents may need to slide easily up and down through more or less intense levels of care. Satellite support groups should be created to increase accessibility to ongoing care. Hours need to accommodate school in order to get individuals' education back up to speed. Residential treatment should be relied upon only when absolutely necessary, either because of an adolescent's continued life threatening behaviors or a seriously abusive home environment, and could be offered by a few regional centers serving the network of adolescent outpatient clinics. Liaison between outpatient clinics and school-based SAPs needs to be ongoing and fluid in order to create a true continuum of care in which each level collaborates effectively with the others.

Outpatient clinics need to offer a wide range of services not available at the SAP level. Substance abuse evaluations and several weeks of intensive recovery work need to be available up front. Comprehensive psychiatric and neuropsychological evaluations need to be available when needed. Treatment of comorbid psychiatric disorders, found in up to 60% of substance abusing adolescents, need attention. Detoxification and medication management needs to be provided directly, or supervised by a physician.

Group therapy, including peer, multifamily, relapse reduction, and life skills should be at the core of treatment. Individual and family therapy require highly trained clinicians, especially when a history of trauma exists. An environment sensitive to cultural and gender issues needs to be maintained. Confidential, privacy-protected, and on-site oral drug testing needs to be used for therapeutic purposes only. Telehealth capacity is needed in rural areas and whenever transportation is problematic. Specialists in outreach need to make contact with school and treatment dropouts. An electronic medical records system is needed to tie the treatment system together into a seamless whole and to facilitate outcome studies to identify areas for treatment improvement.

Staff in adolescent treatment clinics need to be better trained, and thus better paid, than in adult treatment programs. In addition to understanding substance abuse disorder, the complexities of adolescent development need to be integrated into treatment. The work can be grueling, intense, and too often deeply painful when a young person relapses or overdoses. But it can also be profoundly rewarding when clinicians help patients survive adolescence and successfully navigate their treacherous journey into adulthood. These victories ripple out into the world and live on beyond our own lifetime.

It remains to be seen how much California accomplishes on behalf of its adolescents with its eventual influx of $500 million from marijuana tax revenue. A new gold rush is on and different interests, agencies, and entrepreneurs all are competing for their share.

The struggle to spend this money wisely will be ongoing. But, whatever system of treatment emerges, individual clinicians will be most helpful if they embody the principles of motivational interviewing and the stages of change framework to engage their patients solidly in an empathic, healthy relationship. That fundamental task confronts clinicians wherever in the world, and in whatever system, they practice their craft.

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Chapter

14 Sociopolitical History of Marijuana and America's War on Drugs

Although today California is seen as a cradle of liberal marijuana politics, it was once a cradle of anti-drug legislation, including marijuana. Understanding early attitudes toward immigrants helps explain the earliest parts of this history. The California gold rush of 1849 created a need for cheap labor for the mining industry. As a consequence, 24,000 Chinese came through San Francisco between 1849 and 1853. The "yellow peril" was so reviled as sub-human by whites that Congress closed the borders to Chinese by passing the Chinese Exclusion Act in 1882, the only U.S. law ever passed to prevent immigration and naturalization on the basis of race.

The first known shipment of Chinese opium arrived in San Francisco in 1861 aboard the clipper *Ocean Pearl*.[1] The opium dens that sprang up in San Francisco's Chinatown became a source both of repulsion and fascination for the white population. Lurid stories in the San Francisco Chronicle tarred all Chinese as lacking the self-controls of mind and body that was central to the identity of the nineteenth-century white middle class. As a result, in 1875, San Francisco passed an ordinance against opium dens – one of the first anti-narcotics laws in the U.S.[2]

A surge of progressive social activism from the 1890s to the 1920s was changing the role of government in America in an effort to eliminate problems caused by industrialization, urbanization, immigration, and corruption. California's Board of Pharmacy led the way in 1907 by adding a prohibition against the nonprescription sale of opium, morphine, and cocaine to California's poison laws seven years before the U.S. Congress passed the Harrison Act restricting the sale of narcotics. Aggressive policing soon pioneered many modern techniques of drug enforcement, including undercover agents and informants, criminalization of users, and anti-paraphernalia laws.

Although the introduction of marijuana into the U.S. is generally acknowledged to have occurred via Mexicans coming through El Paso and Caribbean sailors entering Galveston, Houston, and especially New Orleans, the drug came to California's attention through a group of Punjabi Sikhs arriving in San Francisco as indentured laborers in 1910 and reported to be bearing "hasheesh." The exotic turban-wearing foreigners willing to work for low wages were immediately despised. A member of the Board of Pharmacy, Henry J. Finger, wrote in 1911, "Within the last year we in California have been getting a large influx of Hindoos and they have in turn started quite a demand for cannabis indica; they are a very undesirable lot . . ."[3]

By the next state legislative session in 1913, news about "marihuana" filtering north across the border from Mexico was being reported. Cannabis, though still a minor issue, was seen as another evil associated with the threat of alien immigrants. Laborers entering the Southwest during the Mexican Revolution were tainted by images of Pancho Villa's bandoliered men singing:

La cucaracha, la cucaracha,
ya no puede caminar;
porque no tiene, porque le falta,
marihuana que fumar.

"The cockroach, the cockroach,
it can't walk anymore
because it doesn't have, because it's
lacking
*marijuana to smoke."**

Finger gained unanimous support for prohibiting the possession of "extracts, tinctures, or other narcotic preparations of hemp, or loco-weed." Two years later (1915), the law was expanded to include forbidding the sale of "flowering tops and leaves . . . of hemp."[4] Multiple states soon followed suit.

It is useful to put these events into broader context. The progressive era's belief in big government's ability to solve social problems was at its peak with Woodrow Wilson's inauguration in 1913. America's entry into World War I in 1917 intensified xenophobic dislike of Germans and their association with beer (Pabst, Schlitz, Blatz, and Miller). The long-struggling Temperance Movement came to fruition when Congress passed the 18th amendment to prohibit the production and sale of alcohol in 1917 and it was ratified by the states in 1919. For perspective on what many mistakenly see as a uniquely American folly, it should be noted that Russia began a limited version of prohibition in 1914, Norway instituted complete prohibition in 1917, and Finland followed in 1919. America and other countries in Europe were about to discover the dangerous unintended consequences of legislating against popular behavior.

The 18th amendment went into effect at the beginning of 1920, the same year Al Capone arrived in Chicago.[5] Organized crime enjoyed the corrupting power of immense wealth as Capone was soon earning over $100 million annually. Bootlegging profits led to organized crime developing both political and violent

* This is probably the source of using "roach" as slang for the last portion of a marijuana joint where the resin is most concentrated.

physical power nationwide. Once any drug is made illegal, it creates a niche for criminal activity. Criminals selling the drug come into possession of large sums of cash that need to be protected. If another drug dealer steals your cash, there are no police to call. You cannot deposit your funds in a bank for safekeeping without first laundering the cash through "legitimate" businesses. Protection of turfs and profits necessarily needs to be outside the legal system. Power, force, and violence are the only tools available to protect one's interests from others also operating outside the law. In the end, the boost to organized crime created by criminalizing alcohol was too great to control. After the 21st amendment repealed prohibition in 1933, organized crime needed to look toward other opportunities, often turning to those created by other illegal drugs.

Because neither the 18th amendment nor the Volstead Act passed to enforce prohibition outlawed possessing or drinking alcohol, those rich enough to have bought the inventory of wine and liquor stores before prohibition went into effect were free to consume it over the ensuing years. The same was not true for cannabis in California, where cannabis possession and use remained a crime. Following passage of the Poison Law's prohibition of cannabis, except by prescription, agents launched a crackdown in a Mexican neighborhood of Los Angeles in 1914 to destroy what the Los Angeles Times called two "dream gardens" of "marihuana." One quarter of drug arrests in Los Angeles were for marijuana in 1925, at which time possession itself had become punishable by up to six years in prison. By 1930, marijuana accounted for nearly 60% of drug arrests in Los Angeles, and 26% statewide.[6]

A major event in the history of enforcing marijuana prohibition was set in motion by passage of the 21st amendment repealing alcohol prohibition in late 1933. It is useful to review the dynamics leading to alcohol prohibition's repeal in order to understand how the same dynamics are present today in regard to marijuana. The federal government never had the resources to enforce alcohol prohibition, despite developing an enforcement unit within the Treasury Department and the heroics of Eliot Ness, who started working with Chicago's "Untouchables" in 1927. Most of the enforcement of prohibition, however, was left to states to organize and finance. Not all states were equally enthusiastic. Maryland was unique in its reaction to prohibition. Despite voting to ratify the 18th amendment, Maryland was the only state to *never* pass a state enforcement act and Baltimore continued the distribution, sale, and consumption of illicit alcohol throughout prohibition under the auspices of city and state government.[7] By 1925, in New York City alone, there were anywhere from 20,000 to 100,000 speakeasy clubs.[8] When Gustav Boess, the Mayor of Berlin, visited in the fall of 1929, he asked the New York mayor when prohibition was going into effect![9]

With the country mired in the Great Depression by 1932, creating jobs and recapturing tax revenue by legalizing the liquor industry had an undeniable appeal. The Democratic Party adopted a plank in its convention platform calling for the repeal of prohibition. In a campaign speech Franklin Roosevelt said, "I need not point out to you that general encouragement of lawlessness has resulted; that corruption, hypocrisy, crime and disorder have emerged, and that instead of restricting, we have extended the spread of intemperance. This failure has come for this very good reason: we have depended too largely upon the power of governmental action . . ."[10]

The states had already begun to rebel. A 1929 referendum in Wisconsin repealed its enforcement under the Volstead Act.[11] In 1933, Michigan reversed its own prohibition

laws and called for the repeal of the 18th Amendment. After Roosevelt's inauguration, Congress passed the 21st amendment repealing prohibition. What was often called "The Noble Experiment" came to an end on December 5, 1933 when Utah became the 36th state to ratify its repeal. Legend has it that Franklin Roosevelt celebrated the repeal of prohibition by enjoying a dirty martini, his preferred drink.

Alcohol prohibition failed on many fronts. It was supposed to decrease crime associated with alcohol and instead led to the flourishing of organized crime, violence, and corruption. It led to pervasive disrespect for authority as millions of everyday people disobeyed the law. Drinking may have actually increased, too often with unsafe liquor, although the incidence of cirrhosis did decline. And states lost critical tax revenue at a time when the depression strapped government financially. The one thing alcohol prohibition did not do was criminalize individuals who drank. Unlike the prohibition of marijuana, which was soon to receive more attention, alcohol prohibition did not incarcerate people for mere possession of the drug.

Enter Harry J. Anslinger. From 1917 to 1928, Anslinger worked against international drug trafficking. In 1929, he became an assistant commissioner in the Treasury Department's Bureau of Prohibition, where turmoil and re-organizations provoked by failure to enforce prohibition led to Anslinger's appointment as the founding commissioner of the Treasury's Federal Bureau of Narcotics (FBN) in 1930. Anslinger initially claimed that cannabis was not a problem, did not harm people, and "there is no more absurd fallacy" than the idea it makes people violent. During its first few years, the FBN minimized the marijuana problem, which Anslinger believed was best dealt with by the 24 states that had already outlawed it. He is reported as complaining that marijuana grows "like dandelions," and trying to stamp out a plant that flourished everywhere in the world except Antarctica and the Arctic Circle seemed like a dubious proposition. With only 300 special agents to fight heroin and cocaine, attacking a common weed seemed both demeaning and quixotic to Anslinger.

Perhaps it was mission creep for Anslinger's bureau after alcohol prohibition ended, but his mind soon changed. He began a campaign for cannabis prohibition by collecting reports of violent crimes allegedly committed under the influence of marijuana, often repeating the lurid tale of Victor Licata's ax murder of his family in 1933. In a magazine article Anslinger wrote that the police found Licata ". . . in a daze . . . He had no recollection of having committed the multiple crimes. The officers knew him ordinarily as a sane, rather quiet young man; now he was pitifully crazed. They sought the reason. The boy said that he had been in the habit of smoking something which youthful friends called 'muggles,' a childish name for marijuana."[12] In the same article he stated that it was this "unprovoked crime some years ago that brought the first realization that the age-old drug had gained a foothold in America." He concluded that "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 . . . No one knows, when he places a marijuana cigarette to his lips, whether he will become a joyous reveler in a musical heaven, a mad insensate, a calm philosopher, or a murderer . . . " As for the truth about Victor Licata, despite a pre-existing history of mental illness and psychiatric examinations shortly after the murders that never mentioned marijuana use, the label "ax-murdering marijuana addict" was fixed in the public's mind largely by the sensational "yellow journalism" typified by William Randolph Hearst's newspapers.

Overt, blatant racism that should embarrass us all, with accusations of sexual degeneracy mixed in, also played an important role in demonizing marijuana. According to legend, Anslinger told a Narcotics Bureau conference that "Reefer makes darkies think they're as good as white men . . . [and] the primary reason to outlaw marijuana is its effect on the degenerate races."[13] Better documentation exists for his having written that "Colored students at the University of Minnesota partying with (white) female students, smoking [marijuana] and getting their sympathy with stories of racial persecution. Result: pregnancy"[14,15] and "Two Negros took a girl fourteen years old and kept her for two days under the influence of hemp. Upon recovery she was found to be suffering from syphilis."[16]

At the same time, Hearst was using his nationwide conglomerate of 28 major newspapers, 18 magazines, radio stations, and motion picture companies to beat the drum of fear about Mexican immigrants. Perhaps his loss of 800,000 acres of timberland and 60,000 head of cattle in northern Mexico during the Mexican Revolution added fuel to his hatred.[17] His *San Francisco Examiner* wrote that:

> By the tons it is coming into this country – the deadly, dreadful poison that racks and tears not only the body, but the very heart and soul of every human being who once becomes a slave to it in any of its cruel and devastating forms . . . Marihuana is a short cut to the insane asylum. Smoke marihuana cigarettes for a month and what was once your brain will be nothing but a storehouse of horrid specters. Hasheesh makes a murderer who kills for the love of killing out of the mildest mannered man . . .[18]

Other Hearst papers wrote "THREE-FOURTHS OF THE CRIMES of violence in this country today are committed by DOPE SLAVES – that is a matter of cold record."[19] America was reading powerful stuff.

Once Anslinger was on board with attacking marijuana, he understood that the likelihood of prohibitory legislation increased if the substance in question was associated with ethnic minorities. Thus, Anslinger claimed in 1936 that 50% of violent crimes committed in districts occupied by "Mexicans, Greeks, Turks, Filipinos, Spaniards, Latin Americans and Negroes may be traced to the use of marihuana."[20] The headlines and the plotlines were anti-drug and anti-crime, but the subtext was always about race. Congress held only two one-hour hearings when it considered the Marijuana Tax Stamp Act in 1937 before passing the bill that created marijuana prohibition. Because the Treasury Department can only advance bills about taxation, the act technically permitted the sale of marijuana, but only with a $100/ounce tax and purchase of a marijuana tax stamp – which never became available. On the day marijuana prohibition was enacted, October 2, 1937, the FBI and Denver police arrested Samuel R. Caldwell, who became the first marijuana seller convicted under U.S. federal law. Judge Foster Symes said, "I consider marijuana . . . far worse than the use of morphine or cocaine. Under its influence men become beasts. Marijuana destroys life itself. I have no sympathy with those who sell this weed." He then sentenced Caldwell to four years of hard labor in Leavenworth Penitentiary and a $1000 fine. Caldwell's customer, Moses Baca, aged 26, received 18 months incarceration for possession of two joints.[21]

Caldwell and Baca may have been the first to be incarcerated under federal prohibition of marijuana, but many, many more were to follow. It was also around this time that the infamous movie *Reefer Madness* debuted. Initially named *Tell Your*

Children, a religious group funded the 1936 movie to warn parents of marijuana's evil. Passage of the marijuana Tax Act prompted a Hollywood producer to purchase and re-cut the film to add to its list of exploitation movies in 1938. The movie industry's self-imposed Motion Picture Production Code (1930–1968) prevented portrayal of any morally dubious behavior. Film makers got around this limitation by producing morally self-righteous movies, filled with sexually provocative themes and warning of juicy dangers. For example, *Assassin of Youth* (1937) promised "Wild-Mad Thrills" and *The Burning Question* (1938) screamed about "The Love Weed – Women cry for it! Men die for it!" As it turned out, *Reefer Madness* bombed at the box office despite its efforts to titillate audiences, but it later became a cult classic for marijuana users in the early 1970s. In truth, *Reefer Madness* was less of an anti-marijuana movie than one of many that used marijuana as a vehicle for exciting audiences' prurient interests.

While Anslinger had no direct connection to *Reefer Madness*, he did take special interest in criticizing and prosecuting individuals in the music industry – especially jazz musicians. An often quoted (but not fully documented) expression of his distaste for jazz that is consistent with his actions has Anslinger saying, "Most marijuana smokers are colored people, jazz musicians, and entertainers. Their satanic music is driven by marijuana, and marijuana smoking by white women makes them want to seek sexual relations with Negroes, entertainers, and others."[22] There was some truth to his claim that black jazz musicians coming out of New Orleans enjoyed their weed – Cab Calloway ("Reefer Man"), Nat King Cole, Louis Armstrong ("Muggles"), Thelonius Monk, Ella Fitzgerald ("When I get low I get high"), and even the white clarinetist Benny Goodman ("Texas Tea Party," using a common slang for marijuana). Louis Armstrong was arrested in California in 1930 for marijuana possession but continued to use what he called "gage" before performances and recording sessions.

America's drug policy took a crucial turn into a political cul-de-sac in 1971 when President Richard Nixon declared drug abuse "public enemy number one" in a special message to Congress. Nixon had been in law school at Duke when Congress passed the Marijuana Tax Stamp Act. Thirty-four years later marijuana-smoking war protesters and black rage were complicating his presidency as much as the failing conflict in Vietnam. In what appears to be a cynical tactic, Nixon waged war on drugs in part to suppress these opposing forces. Presidential aide John Erhlichman was later quoted as saying, "We knew we couldn't make it illegal to be either against the war or black, but by getting the public to associate the hippies with marijuana and blacks with heroin, and then criminalizing both heavily, we could disrupt those communities."[23] (As one must often do when highlighting Nixon's dark side, an objective appraisal of this complex man needs also to acknowledge his administration's establishment of the first methadone clinics and creating the National Institute of Alcohol Abuse and Alcoholism).

The American prison population rose slowly for the next decade. Then, in 1981, the War on Drugs mutated into a War on Drug Users when President Ronald Reagan acknowledged that fighting the supply side of the Drug War was failing. He said, "It's far more effective if you take the customers away than if you try to take the drugs away from those who want to be customers."[24] "Getting tough" on drugs now meant getting tough on drug users by holding them fully accountable for illicit drug trafficking and

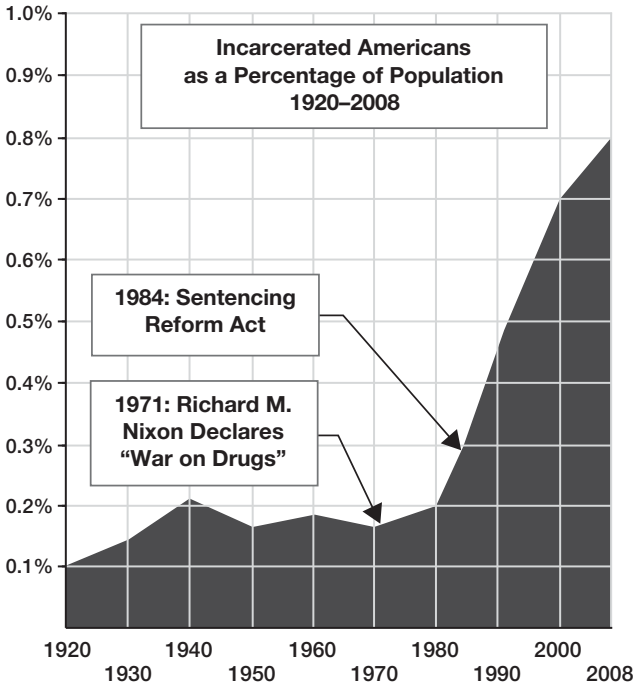

Figure 14.1 Explosion of prison population during U.S. War on Drugs. Source: J. Austin and A. D. McVey. The 1989 NCCD prison population forecast: the impact of the war on drugs. San Francisco: National Council on Crime and Delinquency, 1989. www.ncjrs.gov/pdffiles1/Photocopy/122794NCJRS.pdf

punishing them accordingly. Incarceration became a growth industry, including for-profit prisons, as the prison population exploded (Figure 14.1). In the 1980s, while the number of arrests for all crimes had risen by 28%, arrests for drug offenses rose 126%.[25]

The U.S. eventually incarcerated 25% of the world's prisoners despite having only 5% of the world's population. America has imprisoned 2.3 million of its citizens at an annual cost of $80 billion.[26] According to the Drug Policy Alliance, 2015 saw 1.25 million arrests for simple drug possession, 575,000 of which were for marijuana.[27] Although it is rare for people to be imprisoned for marijuana possession today, over 200,000 students have lost eligibility for financial aid due to a previous drug conviction. Countless others have experienced difficulty obtaining employment because of a history of drug arrest, while others on parole have too frequently been returned to prison for dirty urines from marijuana use.

The Drug War has disproportionately impacted African-Americans. According to Human Rights Watch, in 1998, African-American drug users made up 35% of drug arrests, 55% of convictions, and 74% of people sent to prison for drug possession crimes. Nationwide, African-Americans were sent to state prisons for drug offenses 13 times more often than other races, even though they only comprised 13% of regular drug users.[28] Two graphs summarize the disparity between enforcement of marijuana laws on blacks and whites, both of whom use marijuana at approximately the same rates (Figure 14.2), but blacks get arrested almost four times more often (Figure 14.3).

The War on Drugs has been a disaster for the same reason that the Spanish Inquisition failed. War – especially when a country goes to war against its own people – is inevitably doomed as a domestic policy for changing behavior. The Spanish imported

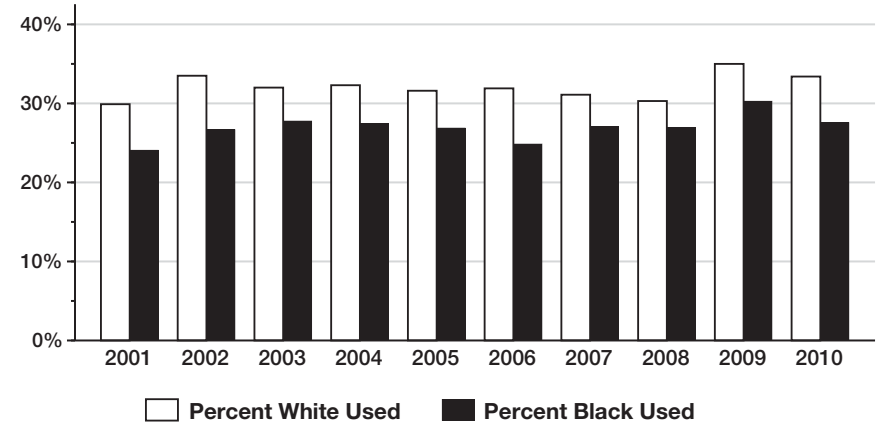

Figure 14.2 Use of marijuana by race. Source: Ezekiel Edwards, director, Criminal Law Reform Project; Will Bunting, fiscal policy analyst; and Lynda Garcia, Soros Justice Fellow. The War on Marijuana in Black and White, American Civil Liberties Union 2013, Figure 22, Page 67. https://pdfs.semanticscholar.org/cf86/2f2cd14a07da0df5258d17c0f138851510f6.pdf?_ga+2.38178275.1302597496.1566485316-1327173705.1565891622 (Accessed August 22, 2019.)

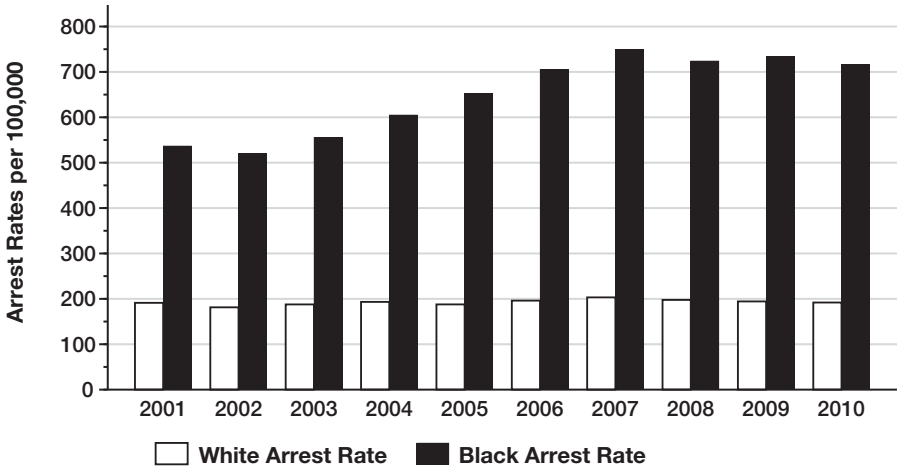

Figure 14.3 Arrest rates for marijuana possession by race. Source: Ezekiel Edwards, director, Criminal Law Reform Project; Will Bunting, fiscal policy analyst; and Lynda Garcia, Soros Justice Fellow. The War on Marijuana in Black and White, American Civil Liberties Union, June 2013, Figure 10, p 48. https://pdfs.semanticscholar.org/cf86/2f2cd14a07da0df5258d17c0f138851510f6.pdf?_ga+2.38178275.1302597496.1566485316-1327173705.1565891622 (Accessed August 22, 2019.)

the Crusades as a policy against its own nonbelievers. America tried to adapt a belligerent policy of warfare to control its own "deviant" citizens which only perpetuated an underclass, created a lucrative niche for drug dealers, and fostered disrespect for the law. The latter two results repeated the failures of alcohol prohibition. In the end, the epitaph for both alcohol and marijuana prohibition has to be the same: Neither

reduced use, while both increased suffering. It is time to learn the lessons of history and set a new course for drug policy, starting with marijuana. Chapter 15 next explores the new strategies for marijuana policy emerging globally and within the U.S. – policy based on public health principles, not on a disingenuous fusion of political power and morality.

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Chapter

15 The Post Drug War Era

The War on Drugs failed. It failed because it did not reduce drug use sufficiently, if at all. It failed because incarceration is arbitrary, too costly, and ineffective except as an advanced course in criminality for prisoners. It failed because it created, in the words of Barry McCaffrey, director of the Office of National Drug Control Policy, an over-populated "American gulag".[1] The War on Drugs failed because it became a War on Drug Users – too often our family, friends, and neighbors. And it failed because it did too little to reduce demand, to treat those in need, to de-stigmatize addiction, or to support recovery.

The tide of public opinion has turned against punishing marijuana users, both in many parts of the world and within increasing portions of the U.S. The public's taste for incarcerating recreational marijuana users has ebbed away. And most have lost their tolerance for the disgraceful racial disparity that the War on Drugs waged. If America tried to re-establish a "zero tolerance" of marijuana use through tough enforcement measures, the resulting level of police intrusion into people's lives and contraction of civil liberties would be unacceptable to most.

A return to aggressive incarceration to suppress marijuana use is, of course, possible. Jeff Sessions, Trump's Attorney General for the first two years, bluntly stated, "good people don't smoke marijuana." This means that nearly half of adult Americans are not good people. What would be the basis for making such a moral judgment? What sense does it make to say that good people drink alcohol but become bad people if they use marijuana? The only way to make sense of this is either to invoke denial as a protective shield against seeing the damage done to the public's health by alcohol or to make a weak distinction between ingesting a substance for the express purpose of its psychoactive effect (i.e., smoking pot to get high) versus drinking a beverage that "incidentally" has a psychoactive effect. The distinction collapses as soon as the arbitrary historical/cultural

condoning of alcohol is removed from the equation. Pharmacologically and psychologically, any distinction is trifling and based on an individual's cultural, moral/religious, or partisan political perspective. Moral/religious standards are important for guiding an individual's behavior but should not be permitted to violate the separation of church and state enshrined in the American Constitution to protect the public's civil liberties from the personal moral/religious judgments of whoever is currently in political power.

During the previous Obama administration, Attorney General Eric Holder created a policy of restrained enforcement of federal prohibition as long as citizens complied with their state's marijuana laws. In the tradition of Supreme Court Justice Louis Brandeis, Holder viewed states as the "laboratories of democracy" for issues having no substantial national unanimity of agreement. In essence, Holder argued for a version of states' rights. The current administration has expressed a desire to reinvigorate anti-marijuana policies reliant on police enforcement, though little action in this direction has taken place. Only the Rohrabacher–Farr amendment (2014) prohibiting the Justice Department from spending funds to interfere with implementation of state medical marijuana laws stands in the way. The arc of history clearly bends toward reform of marijuana policy and will not be stopped by any single administration's nostalgic efforts to turn back the clock to a more muscular approach.

Confidence in the momentum toward a public health approach to marijuana comes from two factors – the waning moralistic motivations at the core of prohibition and the global movement away from punitive approaches to drug use. On a global level, countries are leaving the umbrella created by America's effort to conduct our War on Drugs in other nations. Latin American countries are less likely now to accept military assistance to combat drug production intended for export to the U.S. Uruguay has legalized marijuana and Fernando Cardoso, past-president of Brazil and chair of the 2016 United Nations General Assembly Special Session on Drugs declared the War on Drugs a failure while calling for "an end to the criminalization and incarceration of users together with targeted prevention, harm reduction and treatment strategies for dependent users" in the Global Commission Report (supported by Kofi Annan, UN General Secretary and George Schultz, past U.S. Secretary of State).[2] Portugal eliminated criminal penalties for personal possession of all drugs in 2001.[3,4] And in late 2017, "wild and crazy" Canada became the second country to legalize recreational use of cannabis – clear evidence that the War on Drugs is losing support.

Portugal's experience with decriminalization of drugs warrants close attention. Caitlin Hughes and Alex Stevens, in Australia and the UK respectively, reviewed the evidence to determine whether Portugal's new policy was a "resounding success" or a "disastrous failure," as its advocates and detractors each argued, or somewhere in the middle. Despite requirements of the United Nations conventions on illicit drugs, following a period of escalating drug use undeterred by increasingly harsh criminal penalties, in 2001, Portugal decriminalized possession of *all* drugs, when deemed for personal use, while maintaining criminal sanctions against their manufacture, trafficking, and sale. Drug possession became an administrative offense with a public health response. Prevention, harm reduction, and treatment resources were greatly expanded, including local dissuasion councils staffed by lawyers, social workers, and medical professionals acting as brief interventionists with a focus on encouraging nondependent users to reduce their use and guiding dependent users toward treatment.

The data collected by Hughes and Stevens revealed the following:

- small increases in reported illicit drug use among adults
- reduced illicit drug use among problematic drug users and adolescents
- reduced burden of drug offenders on the criminal justice system
- increased uptake of drug treatment
- reduction in opiate-related deaths and infectious diseases
- increases in the amounts of drugs seized

These results take on even more import when compared to data from the neighboring countries of Spain and Italy. Both neighbors experienced a similar increase in illicit drug use among adults over the same years, making it impossible to ascribe Portugal's small rise to the advent of its decriminalization policy with any certainty. At the same time, Portugal's decrease in drug use among problematic drug users and adolescents as well as the reduced burden on criminal justice were in contradistinction to Spain and Italy's experience. Something is clearly working in Portugal, though it is not clear how much of the benefit derives from decriminalization per se and how much from the expansion of prevention, intervention, and treatment services. Nor is it known how well the same policies would work in more heterogeneous populations.

Closer home to me is the rebellion in the U.S. against the War on Drugs that started in San Francisco in 1991 when 79% of the City's voters, fueled by suffering caused by AIDs, approved a resolution legalizing medical marijuana. State lawmakers passed similar legislation, but the governor vetoed it. Proposition 215, the Compassionate Use Act of 1996, was then placed before state voters and passed with 55.6% of the popular vote, making California the first state to relegalize the use of marijuana products for medical purposes. The vote allowed people with a doctor's letter of recommendation to possess and cultivate marijuana for personal medical use. This put California squarely in conflict with the federal government. A court case (Garden Grove v. Kha) ruling in 2007 that "it is not the job of the local police to enforce the federal drug laws" was reminiscent of Maryland's refusal to enforce federal alcohol prohibition. By the time of this ruling, 10 additional states had legalized medical use of marijuana. Today, medical marijuana is legal in 33 states and counting, as well as the seat of the federal government in the District of Columbia.

Decriminalization of marijuana began state by state in the 1970s on several different levels with the goal of eliminating arrest, prison time, or criminal records for first-time possession of small amounts of marijuana for personal use. Today, in addition to the nine states that have legalized recreational marijuana, 13 states have decriminalized pot by lowering offenses to misdemeanors or infractions similar to a minor traffic violation – a ticket. Multiple studies of the impact of decriminalization have come to the same conclusion as the *British Journal of Psychiatry*, which concluded, "The available evidence suggests that removal of the prohibition against possession itself (decriminalization) does not increase cannabis use."[5] Studies in Australia, the Netherlands, and the U.S. continue to confirm early results found by Monitoring the Future, i.e.:

> *Overall, the preponderance of the evidence which we have gathered and examined points to the conclusion that decriminalization has had virtually no effect either on the marijuana use or on related attitudes and beliefs about marijuana use among American young people. The data show no evidence of any increase, relative to the control states, in the proportion of the*

age group who ever tried marijuana. In fact, . . . states showed a small, cumulative net decline in annual prevalence after decriminalization.[6]

California twice attempted to be the first state to legalize recreational use of marijuana, in 1972 and 2010. The first attempt lost with a 66.5% No vote. The second, called the Regulate, Control & Tax Cannabis Act, lost with only a 53.5% No vote despite being a deeply flawed proposition that incorrectly stated as scientific fact that marijuana is not addictive – as though a law could make it so. Advocates' primary argument focused on the financial benefits of increased tax revenue for the state and savings by law enforcement – both of which had been winning arguments in favor of repealing alcohol prohibition. The near passage of this proposition activated many around the state to assume the next legalization proposition would likely pass. They began thinking seriously about the best framework for such an eventuality.

My colleague, Dr. Peter Banys, and I prepared a document in 2011 for the California Society of Addiction Medicine called *Youth First* outlining elements we thought should be included in any future policy legalizing marijuana.[7] We began by asserting that youth are at greatest risk of harm from marijuana use and already had unlimited access to marijuana in California but very limited access to treatment when needed. Addiction medicine had long argued that treatment works better than incarceration for reducing drug abuse, and public health principles rather than enforcement methods should be at the core of drug policy. Our clinical experience had also led us to the belief that marijuana prohibition is not necessary for adult public health protection. We proposed a framework of constructive regulation of marijuana to achieve the following goals:

- Limit access to marijuana for those under 21
- Keep youth in school
- Provide schools with resources to identify and help students using marijuana
- Construct a community-based evaluation and intervention system to address youth under 18 who are using marijuana
- Provide treatment to youth who have become dependent on marijuana

Our underlying concern was that the imminent end of marijuana prohibition not make the same mistake that was made with ending alcohol prohibition. Every industry should be taxed in such a manner that sufficient revenue is generated to mitigate damage to the public caused by that industry's product. Business should not be permitted to make a profit while passing the expense of repairing unintended collateral damage on to the public. In the case of alcohol, tax revenue from beer, wine, and liquor has never come close to paying for the damage done to some customers, their families, traffic victims, and places of employment. If a new industry were to be created for the production and sale of marijuana, it would be essential to set taxation policy at appropriate levels at the outset to pay for potential damage it causes. In the case of marijuana, that damage usually begins with underage use. If the opportunity to achieve this goal at the outset is lost, it is unlikely to be achieved in the future.

The *Youth First* report identified SAPs as the best example of a mechanism proven to support youth in their primary "workplace." Just as EAPs bring confidential services into adults' workplace, SAPs can provide on-site help to keep youth in school. As long as a student's educational progress continues, future prospects for healthy development are safeguarded. SAPs bring prevention programs to where they are most needed and can intervene early when treatment becomes necessary.

It is a basic fact that, if adults had no interest in marijuana, youth would have far less access to pot. Adult use bears almost complete responsibility for the "attractive nuisance" that readily available marijuana presents to youth. Therefore, those adults who use marijuana should bear the primary responsibility for funding services needed by marijuana-using youth. Taxing the marijuana industry, not to fill the coffers of a state's general fund, but rather to prevent and treat the damage *already* being done to a significant minority of youth, should be the goal of marijuana tax policy under a regulated market. A two thirds majority of addiction doctors in CSAM voted their agreement with the principles and recommendations *Youth First* proposed.

At the same time in 2011, the California Medical Association (the AMA state chapter) was developing its own recommendations for marijuana policy reform. The California Medical Association, representing 43,000 California physicians, formally called for regulating recreational marijuana in a manner similar to alcohol and tobacco, with tax revenue dedicated to regulation, enforcement, and education. Their report identified educational campaigns targeting different demographics with the goal being to reduce cannabis use among children, adolescents, and young adults.

In November 2012, Colorado and Washington State voters went first, and the legal sale of marijuana began in Colorado on January 1, 2014. The first $40 million of tax revenue from marijuana sales was directed toward school construction projects (but not teachers, books, or counselors), while local communities used their share of the revenue to help address homelessness, patch roads, secure water rights, and fund an array of other civic projects.[8] The bulk of sales tax goes into the state's general fund to be used at legislators' discretion, including enforcement of marijuana regulations, prevention, and treatment. For perspective, it is useful to view the tax revenue from retail sales of marijuana as another "sin tax." In fiscal year 2015–16, Colorado collected $55 million from tobacco, and $43 million from liquor excise tax, $103 million from casinos and $129 million from recreational marijuana.[9]

Washington State did not have the robust medical marijuana industry found in Colorado to build upon and began retail sales of marijuana more slowly, starting in mid-2014. Because of concern youth would increase their use Washington directed tax revenues more narrowly to fund substance abuse prevention and treatment programs, youth and adult drug education, community health care services, academic research, and evaluation of the effects of marijuana legalization. In fall 2016, over 230,000 students participated in the Washington State Healthy Youth Survey. Rates of teen marijuana use continued to remain steady, as they had for the previous decade, despite the changing legal landscape.[10]

Colorado youth appear to have shown a similar non-response to legalization. A 2015 Healthy Kids Colorado Survey graph (Figure 15.1) shows that 24.8% of high school students had used marijuana in the previous month at the beginning of the state's boom in medical marijuana stores in 2009. Past month use fell to 22% in 2011, the year before legalization was approved. The 2013 survey found that 19.7% of teens had used marijuana in the past month. In 2015 that number was 21.2%, while the national average was 21.7%. Teen use in Colorado has remained relatively consistent, as measured by the state's standard survey methods throughout its transition to legal marijuana.[11]

Although any data from Colorado and Washington State is far too preliminary to draw long-term conclusions, advocates of marijuana legalization in California were encouraged. Armageddon had not occurred in either state, and the federal government

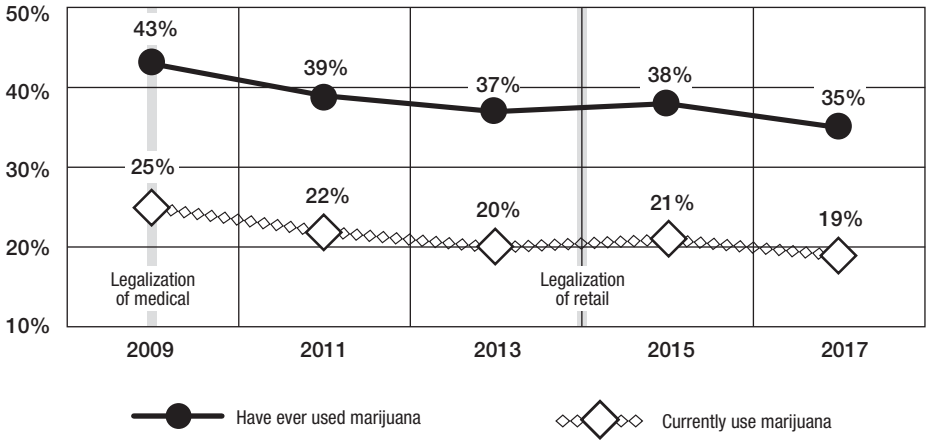

Figure 15.1 Colorado youth marijuana use 2009–2017.
Source: Data Brief: Colorado Youth Marijuana Use 2017, The Healthy Kids Colorado Survey. https://drive.google.com/file/d/1M3XdmqznZDl2y6D7Hz6iDGwTFTHSGrtP/view

was keeping its distance. In fact, Eric Holder clarified the following federal enforcement priorities that states legalizing marijuana would have to meet if they were to avoid interference by the Department of Justice:[12]

- Prevent distribution of marijuana to minors
- Prevent marijuana revenue from funding criminal enterprises, gangs, or cartels
- Prevent marijuana from moving out of states to where it is illegal
- Prevent use of state-legal marijuana sales as a cover for illegal activity
- Prevent violence and use of firearms in growing or distributing marijuana
- Prevent drugged driving or exacerbation of other adverse public health consequences associated with marijuana use
- Prevent growing marijuana on public lands
- Prevent marijuana possession or use on federal property

I had the privilege of serving on the Blue Ribbon Commission on Marijuana Policy convened by California's then Lieutenant Governor Gavin Newsom and the American Civil Liberties Union of Northern California to facilitate a comprehensive understanding of various policy questions related to the possibility of legalizing, taxing, and regulating marijuana for adults in California. The commission also endeavored to identify the pros and cons of various approaches to improving the state's marijuana policies, and to disseminate this information to California voters, policymakers, and "those likely to fund and draft a ballot initiative to tax and regulate marijuana."[13] In other words, the commission was designed to get out in front of the initiative that was highly likely to appear on the 2016 California ballot to legalize marijuana. Given that polling data indicated voters were likely to approve any such initiative, it seemed important to assert every possible influence to assure that the new law would be as well thought out and rational as possible. Leading policymakers, public health experts, and academics formed three work groups: Youth Education, Prevention and Treatment; Public Safety; and Regulatory and Tax Structure. As co-chair of the Youth work group, I focused attention

not on whether California should legalize marijuana, but rather on what elements needed to be in the law to provide the best possible protections for youth if legalization passed. I viewed the task as one of *realpolitik*, i.e., formulating policy based on the circumstances and factors "on the ground" rather than explicit ideological notions. A series of briefs reviewing the scientific literature formed the basis for our Youth work group conclusions.

The Youth Education, Prevention and Treatment policy brief,[14] largely adopted in the Blue Ribbon Commission's final report[15] (*Pathways Report: Policy Options for Regulating Marijuana in California*) emphasized that, if sufficient funding from marijuana tax revenue was effectively dedicated to services for youth, it could close many gaps in community-based support for youth already at risk. If policymakers had the will, universal availability of school-based SAPs and community-based treatment centers could become a reality throughout California. In addition, rigorous restriction of marketing practices directed toward youth need to be implemented. A revamping of marijuana education to stress science-based health-related reasons for delay and moderation, rather than legal consequences, was also needed.

Fortunately, some of the authors of what eventually became Proposition 64 to legalize recreational marijuana were open to the Blue Ribbon Commission's recommendations and Dr. Banys and I were able to meet with a lawyer at the Drug Policy Alliance who was involved in drafting the new law. We argued that many opponents of the proposition would see the benefit of including funds to build SAPs as the locus for education, prevention, early intervention, and referral to a well-funded adolescent treatment system. At the same time, we argued that use of the bulk of tax revenue had the potential for improving what was already a bad situation for those adolescents currently being harmed by marijuana under present policies. To our surprise and delight, when we were shown a draft of the proposition, we discovered that a full 60% of revenue above the necessary expenses for administering regulation of the new industry was to be placed in a Youth Education, Prevention, Early Intervention and Treatment Account to be administered by the Departments of Health Care Services, Public Health and Education. In the words of the legislation, funds are intended for "programs for youth that are designed to educate about and to prevent substance use disorders and to prevent harm from substance use . . . The programs shall emphasize accurate education, effective prevention, early intervention, school retention, and timely treatment services for youth, their families and caregivers."[16] Not only is funding provided for the treatment of all adolescent substance abuse, and not merely marijuana, but the estimated revenue for youth services could eventually amount to $500 million annually! Half a billion dollars, ***if*** *effectively spent*, could possibly prevent and treat more suffering than marijuana legalization would cause.

I am clear that my influence on the framework of marijuana legalization in California has been minor. I served as only one voice among many carrying the message that youth need effective protection and tax revenue needs to be committed primarily to youth services. The commitment of then Lieutenant Governor Gavin Newsom (now Governor Newsom) to this message carried much of the weight. If legalization advocates were going to maintain his support, they needed to adopt this message as well. Whether California's Adult Use of Marijuana Act ultimately proves to be a net benefit for the state will depend on how wisely it is implemented. No law can be written to prevent every unintended consequence or to meet every eventuality that will be encountered. Improvements were being suggested even before

the Bureau of Cannabis Control was up and running, as were efforts to ease regulations on the nascent marijuana industry. But the 64-page law is a good start and now the devilish details of implementation must be diligently attended to. I have had the privilege of being a member of California's Cannabis Advisory Committee, which provides a front seat to witness the difficulty of converting what has been an underground industry for generations into a legitimate private enterprise. The road toward full implementation is strewn with obstacles, each of which has to be identified and studied before it can be remedied or eliminated. It is taking time to fine-tune the law so that legitimate licensed businesses have the advantage over lingering, and still thriving, underground dealers.

Public health concerns remain. For example, while Proposition 64 outlaws marketing attractive to youth, there is no effective mechanism for identifying illegal marketing practices or enforcing their prohibition. Strict enforcement will be especially important for the evolving regulation of high potency products, many of which take the form of candies, baked products, and drinks (juice and soda) that are appealing to children and young people. States legalizing marijuana need to extend all restrictions on youth-oriented tobacco and alcohol advertising and promotion to cannabis products. I believe the California Attorney General should appoint a permanent task force dedicated to monitoring the marijuana industry to enforce restrictions on practices attractive to youth. Special Hazard Warnings need to be posted on edible, drinkable and vaping packaging, as well as on all advertising, regarding the dangers of accidental ingestion by children and developing addiction with excess use. Funding should be dedicated for collecting data on emergency department presentations of cannabis toxicity syndromes.

Drug prevention and education programs focused on marijuana will have to undergo thorough revision to improve science literacy regarding marijuana. Messages directed toward adults will need to stress responsible use and provide guidelines for recognizing overuse. Rather than reminding the public of the threat of arrest or fines as major inducements to avoiding use of marijuana, public health efforts need to provide realistic science-based information about the effects of excessive use. This approach should eventually lead to a better informed public, capable of making decisions based on health concerns rather than fear of punishment. The emphasis needs to be on helping individuals know their own limits, and to recognize when they have exceeded safe levels of use. While marijuana will remain illegal for everyone under 21, public health messages will have to stress the science-based reasons for delaying use. The laws prohibiting use under 21 are not morality-based or arbitrary exertion of adult control. Just as the risk of underage driving is too great to be permitted below a proscribed age, so too is the risk of underage use of marijuana. Perhaps we will eventually determine that setting the legal age at 21 is overly conservative, but exercising abundant caution at the beginning of legalizing marijuana is more than justified. The message to those under 21 needs to become more nuanced than "Just Say NO" or "This is your brain on drugs." We need to develop honest messages that promote abstinence during adolescence, offer scientific explanation for the benefits of delaying marijuana use, encourage moderation if abstinence is not chosen, and continually promote personal responsibility for maintaining one's health. Open discussion of the rationale for prohibiting use before 21 years of age and the potential impact of regular use on school performance and family life need to be at the core of prevention. Promoting awareness of how to access recovery and supportive services can prevent further harm to those who use excessively. And referral to drug evaluation services using dissuasion

strategies similar to Portugal's need to be relied on as a response to underage marijuana use rather than punishment.

Most critical in California will be how wisely half a billion dollars dedicated to youth services will be spent. While these funds are specifically intended for "programs for youth that are designed to educate about and to prevent substance use disorders and to prevent harm from substance use," there is already a gold rush to broaden the uses for these funds, including to plug gaps in the current general mental health system. There are calls for devoting funds to Hollywood-produced public service announcements similar to California's successful anti-tobacco ads. Others want to fund a host of after school activities. More grant seekers will come to feed at the trough. The challenge during implementation will be to keep enough pressure on state agencies to continue directing available funds toward building an integrated continuum of care consisting of school-based prevention/intervention SAPs intimately connected to community-based evaluation and treatment centers. Outreach services to school and treatment dropouts also need to be developed. Nothing less will treat those already in need while working to prevent others from requiring treatment and changing school cultures to be more recovery friendly.

California's AUMA has a good chance of creating policy for legalized marijuana without jeopardizing the health of children and adolescents. The single largest barrier to achieving this would be the development of Big Marijuana – the industry equivalent of Big Tobacco – and continuation of an illegal underground market. Once the industry becomes legitimized, it will grow as large as it can. It will lobby as hard as it can. It will donate as much money as it can to legislators friendly to the industry's interests. This is the way of American free enterprise. No one should be surprised by the power the marijuana industry will achieve and no one should cast aspersions on entrepreneurs doing what entrepreneurs do. Proposition 64 is opening a legitimate business niche that they will fill. Stakeholders interested in protecting youth need to protect the intended purpose of AUMA. The industry will naturally fight to loosen regulations and reduce taxes on their products, particularly if the illegal market continues to undercut their profits. Public health advocates need to fight equally hard to regulate the legal industry while law enforcement needs to suppress the illegal underground market.

Ultimately the marijuana industry and child advocates have enough in common that cooperation should be possible. If legalizing marijuana leads to an unacceptable increase in adolescent harm, the industry itself runs the risk of being seen as unacceptable, and many in the industry are fully committed to protecting youth. However, the enthusiasm of some to promote their product as an unquestioned benefit to all, and the lure of large profits, will undoubtedly produce some abuses. The price of protecting youth will be constant vigilance and political assertion. The goal should be achievable with California's AUMA as a framework.

Andrew

He took his seat at the public hearing of the state Cannabis Advisory Committee and prepared to begin his 90 second testimony. The handsome African-American in his mid-thirties was average height with an impressively muscular build. His voice immediately projected the authority that comes from extraordinary experience.

"I run a licensed cannabis dispensary today that permits me to do legally what I spent five years in a federal penitentiary for – support my family by selling marijuana." He paused just long enough for the rest of the room to realize they had stopped breathing. "I am not bitter about this anymore. I understand I broke the law and I served my punishment. Now I am committed, thanks to those of you who helped legalize cannabis in California, to operating a legal business enterprise, despite the difficulty of obtaining licenses, zoning permits, fire inspections, and on and on. I believe in and support the legal cannabis industry."

"What I am bitter about today is the failure of law enforcement to protect my business from the unlicensed, illegal pot shops that keep springing up all around me, sometimes right next door, or across the street. These illegal shops pay no license fees or taxes, so they undersell me by a third. I call local and state law enforcement, but get little response. Even when illegal shops are put out of business after months of my complaining, they pop up with a different name a week later just down the street."

"This is all I ask: If I support the law, why doesn't the law support me? It had better start happening fast or there will be no legal marijuana industry left."

With that he rose and returned to the back of the room to the loudest applause of the day. I will never forget Andrew and the irony of his life as the state tries to move his industry out of the shadows.

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Chapter

16 The Future of Marijuana

The future of marijuana is best seen from 40,000 feet above the fray, away from the noise passing for debate that engulfs us. From this height we see a broad overview that summarizes what has been learned about marijuana and the brain. Our brain is seen as a colony of individual living cells, each capable of independent life if transferred to a petri dish and given nutrients. Genetically similar within each brain, neurons are highly collaborative. These one-celled animals' collective behavior is similar to a flock of starlings in flight, swirling and pulsating in a dazzlingly coordinated cloud, never colliding. Neurons are like a school of a billion herring swimming packed closely together to resemble a silver whale with amazing shape-shifting agility. Our brain's network of neurons passes rhythmic waves of chemical and electric pulses back and forth, coordinating their activity into something far greater than the sum of their parts. Our brain's family of neurons can synchronize their behavior like thousands of fireflies blinking in unison. Billions of sensate single cells – a tribe of neurons – coalesce to form a single sensate organism. Somehow, miraculously, you and me.

The brain is not merely a set of wires twisted into an elaborate electrical circuit. Information does not travel in only one direction from neuron to neuron down fixed pathways. Like the starlings, herrings, and fireflies, interactions between neurons are mutual. Each individual is aware of the others and provides continuous feedback. On the synaptic level, this continuous mutuality is contributed to by the endocannabinoid system's negative feedback to upstream neurons. From the earliest evolutionary development of neuronal connections, 600 million years ago, the endocannabinoid system has been there. From the earliest neural networks, the endocannabinoid system has guided neuronal growth and branching out to each other. About

34 million years ago, somewhere in the steppes of Central Asia[1], the cannabis plant independently developed chemistry that resembles endocannabinoids well before our earliest human ancestors emerged from the great apes. We can only speculate why the cannabis plant alone developed the biochemistry for synthesizing THC, CBD, and its whole array of other cannabinoids, but it undoubtedly endowed some evolutionary advantage on the plant. Perhaps it warded off insects (although insects are the only animal species lacking any cannabinoid chemistry[2]) and foragers, or perhaps it attracted foragers that helped spread its seeds. Once humans discovered the plant's medical and psychoactive properties, its phytocannabinoids created an enormous evolutionary advantage. Like the tulip in early 17th century Holland, humans intervened to breed strains of cannabis with higher levels of THC and CBD than ever previously found in nature.

The ability of THC to mimic our brain's cannabinoid chemistry can be seen as either entirely coincidental and random or as a gift from the gods, probably depending on how much one loves the high marijuana produces. But the fact that so many people enjoy the experience must tell us something important about our endocannabinoid system. CB1 receptors, anandamide, and 2-AG permeate the brain. Indeed, the founder of cannabinoid chemistry, Raphael Mechoulam, says endocannabinoids play a role in almost all of our body's physiological functions. When ingested, marijuana temporarily raises cannabinoid tone and cannabinoid receptors quell activity throughout the brain's other neurotransmitter systems. The effects of this widespread augmentation of negative feedback on neurons using serotonin, dopamine, GABA, glutamate, etc. neurotransmitters is variable and complex. For example, while GABA is an inhibitory neurotransmitter, glutamate is stimulating; and both tend to converge on the same neurons like gas and brake pedals. Both affect a car's speed, though in opposite directions. The ultimate impact of THC's simultaneous negative feedback on both glutamate and GABA – the neuronal gas and brake, respectively – results from altering balances between the two in different portions of the brain. Perhaps low doses of THC preferentially reduce glutamate's stimulating energy, thereby reducing anxiety, while high doses of THC begin impacting GABA's inhibitory energy more, thereby increasing anxiety. This dichotomy could explain THC's biphasic impact on anxiety. The complexities on a granular level are mind-bending, but everyone who gets high experiences the combined effects of THC's negative feedback on the whole panoply of neurotransmitters operating throughout the brain. The flock of neurons as a tribe gives rise to a communal experience and we, as the organism with awareness of this emergent communal experience, tend to register calm, relaxation, hunger, novelty, revived sensory focus, connectedness, forgetting of negative experiences, and sometimes awe, joy, flow, laughter, and the creativity of connecting dots that typically lie outside the box of day-to-day thinking. At the same time, we suffer diminished short-term memory, executive functions (which may be a relief for people with over-active monkey minds), judgment, motor coordination, and reaction times. All of this soon ebbs away unless repeated too soon. When repeated too frequently for our brain to re-establish its normal number of CB1 receptors, endocannabinoid activity falls below normal levels in between episodes of marijuana use. Nearly everyone dislikes feeling the resulting symptoms of cannabinoid deficiency – boredom, anxiety, restlessness, insomnia, and irritability.

The facts described above lead me to conclude that endocannabinoid deficiency is both unpleasant and perhaps even unhealthy, which led evolutionary forces to increase

dopamine levels in the reward center when CB1 receptors, including those inside the reward center, are stimulated.[3] Exercise increases endocannabinoids and releases dopamine in the reward center, as does eating, touch, and sexual activity. This mechanism of dopamine release in the reward center is evolution's way of promoting behaviors important for survival of the species. We see an amplification of this reward when marijuana is ingested. THC stimulates CB1 receptors and large amounts of dopamine are released. THC's stimulation of CB1 receptors to release dopamine in the reward center demonstrates that the endocannabinoid system is *designed* to produce reward, and therefore to promote whatever activity leads to stimulation of the CB1 receptors by anandamide and 2AG. Our brains are hardwired to promote (i.e., reward) maintenance of an adequate, *healthy* level of cannabinoid tone. Proper regulation of stress responses through the hypothalamic–pituitary–adrenal axis depends on a well-balanced endocannabinoid system.

I hope this book has shifted readers' perspective from the cannabis plant to our internal cannabinoid chemistry – from botany to neuroscience – from bud to brain. With enough distance, we can see more clearly that marijuana is merely one possible gateway to our cannabinoid experience, but a poor strategy for achieving healthy cannabinoid tone and the homeostatic balance this is designed to maintain. These experiences are inherent in our brain's structure and chemistry. Just as people value a natural "endorphin high," elevated cannabinoid tone is an enjoyable state, without regard for how it is produced. Relaxation, calm, refreshed sensory awareness, the zing of novelty in all our experience, connectedness, laughter, and awe are all more available when cannabinoid receptors are stimulated. We learned this about our brains only by studying the effects of marijuana. In the process, we also learned that without the endocannabinoid system, marijuana would be nothing, inert, with no effect on us at all – truly just a weed.

Regular use of marijuana might be health sustaining if not for the flies in the ointment – downregulation of receptors with its resulting cannabinoid deficiency state, the distorted priorities resulting from addiction and cognitive and motivational interference in education, employment, relationships, emotional acuity, and risk assessment. THC stimulates CB1 receptors too hard and too long, compared to our natural endocannabinoids anandamide and 2-AG. THC almost certainly activates a different set of signal transduction pathways within presynaptic neurons than our endocannabinoids do. Too frequent use of THC defeats itself by reducing the number of CB1 receptors. The dysphoria of decreased cannabinoid tone results and the demand for external stimulation from marijuana increases to compensate for its lingering after effects. There is literally no effective, or healthy, way to enjoy the effects of marijuana except intermittently, with the optimal frequency needing to be determined on a highly individual basis requiring rigorous honesty with oneself.

The question still begging to be answered is, "What natural behaviors most effectively stimulate the endocannabinoid system?" What can we do to promote good cannabinoid tone? What healthy activities raise anandamide and 2-AG levels to the point of activating the reward system enough to increase the likelihood of being repeated?

A clue to answering this profoundly important question is that physical exercise raises the level of endocannabinoids circulating in the blood.[4,5] Furthermore, exercise-induced increases in circulating endocannabinoids parallel the intensity of mood change.[6] Blocking cannabinoid receptors reveals that the calming and pain reducing effects of exercise stem more from increased levels of endocannabinoids than

endorphins[7], which suggests the celebrated "runner's high" may be more of an endocannabinoid than an endorphin experience. This leads me to wonder what other activities produce a texture of experience similar to marijuana's positive experiences – relaxation, calm, altered perspective, refreshing of sensations, novelty, connectedness and belonging, awe, and joy. These "cannabinoid-based experiences" sound very similar to what many meditation and yoga practitioners describe as the benefits of their practice. After a 10 day meditation retreat, a Yale professor of engineering wrote "*I know that I am existing differently in my world*. I feel more serene, confident, engaged, and thoughtful. I've never felt closer to my partner . . ."[8] Emory University has conducted similar retreats (Vipassana meditation) with over 500 inmates in Alabama prisons. A longitudinal study found substantial differences in prisoners who completed the experience, including enhanced measurements of emotional intelligence and decreased mood disturbances, which researchers concluded holds promise for addressing self-regulation and impulse control.[9,10] Other Emory University researchers have given neuroscientific support to this soft data about focused attention training by reporting fMRI demonstration of plasticity in the attentional networks of experienced versus less experienced meditators.[11]

Another meditator writes, "Upon terminating the meditation session, I would experience a deep sense of peace and relaxation, which would . . . result in a spontaneous and expansive flow of warm and kind feelings, which naturally led to a deep and genuine experience of loving-kindness for all beings."[12] Multiple studies have shown that meditation reduces physiological stress responses, including dose-dependent lower basal levels of cortisol with two to four weeks of meditation practice[13] and meta-analysis confirms that a wide range of meditative techniques successfully reduce physiologic markers of stress.[14] Despite claims on the Internet that meditation increased endocannabinoids, scientific studies of endocannabinoids in meditation still remain unavailable, though it seems reasonable to hypothesize an increase in blood levels given the fundamental role of endocannabinoids in modulating the HPA axis and cortisol levels.

It is entirely possible that a wide variety of techniques for activating and sustaining good endocannabinoid tone will be discovered and developed in the foreseeable future. Research already shows that a meal eaten in pleasant surroundings increases circulating endocannabinoids (unless alcohol is also consumed).[15] Massage techniques such as osteopathic manipulative treatment produce a 168% increase in serum anandamide (while measuring no increase in endorphins).[16] Even neurofeedback technologies may be developed. Do certain forms of music, chanting, or prayer increase endocannabinoid tone?

However, while similarities between the experience of meditation and marijuana exist, serious practitioners of meditation are quick to note important qualitative differences. For example, "Most people respond to smoking weed with slowing the mind. The mind becomes less active and . . . 'dull'. In meditation the mind is pushed into action . . . [and] alertness, not dullness."[17] Perhaps even more importantly, another meditator writes:

> Marijuana "artificially shifts our focus towards the immediate moment", but by sitting high and using it as a crutch to clear your mind how can you build and learn effective habits to use outside of it? Do you want to rely on marijuana for the rest of your life to find a calm center or do you want to accept the more difficult road of building and experiencing these states within your sober self? *Everything marijuana activates and changes about your brain*

> *is completely possible in the realm of sobriety* [author's emphasis]. And if you learn to access that realm by yourself while sober – I think the insights would be a lot more rewarding and fulfilling.[18]

While physical exercise and meditation may sustain good cannabinoid tone, they require time and effort. Smoking a joint is easier and more immediate, reliable, and intense. There are, however, reasons why behaviorally induced cannabinoid experiences are healthier. First, raising anandamide and 2-AG levels naturally through intentional behavior does not lead to the CB1 receptor downregulation seen with THC. Second, behavioral activation of cannabinoid-induced calming is available in times and places where marijuana would be inappropriate. Taking a few cleansing breaths to regain deep internal focus can be done at work, in the middle of an argument with a partner, when stuck in traffic, or even when serving as an expert witness in a trial – all times when firing up a joint, or even inhaling from a vaporizer infused with THC, would be ill advised. Third, exercise, meditation, and yoga clean the lungs while any kind of inhalation introduces potential contaminants. Finally, there is the choice between intensity and depth. THC produces intense experience, while meditation deepens experience. Individuals successfully recovering from addiction usually come to value depth over intensity when choosing sobriety over their drug of choice. If illness warrants a pharmacologic approach to raising cannabinoid tone, medications that reduce enzymes that degrade anandamide and 2-AG, FAAH and monoglyceride lipase (MAGL) respectively, appear more natural. Raising the level of anandamide by interfering with its enzymatic breakdown by FAAH does not downregulate CB1 receptors. According to Daniele Piomelli, ongoing FAAH inhibition raises anandamide levels without causing receptor desensitization or diminishing analgesic or antidepressant effectiveness over time.[19,20] On the other hand, interfering with MAGL does produce tolerance and dependence.[21,22]

What, then, will be the future of marijuana? I believe the path ahead will take at least four different directions. First, the value of seeking cannabinoid-based experiences through behavioral means that naturally activate the endocannabinoid system will be accepted and even promoted for enhancing wellness. While the cannabis plant is a part of the natural world, its constituents are not the same as endocannabinoids and therefore not naturally a part of our nervous system. Natural endocannabinoid experiences – calm, connected, refreshed sensations, and openness to awe – will be seen as desirable and inherently rewarding. Marijuana research provided understanding of the biochemical basis and healthy-sustaining value of experiences that we already like and benefit from fostering. The future will be awash in innovative ways to augment endocannabinoids without downregulating the entire system.

The second future direction for marijuana is as the provenance for a wide array of medications that will soon be available – medications with more effective and more narrowly targeted benefits, with fewer side effects, than what marijuana itself can offer. Medical marijuana dispensaries will initially merge into regular pharmacies as specific formulations and doses become prescription items covered by medical insurance. But as pharmaceutical improvements come on board medical marijuana will eventually morph into nutraceutical preparations sold at health food stores, along with herbal preparations that "may boost endocannabinoids," for people who trust older remedies more than newer cannabinoid-based FDA researched and approved pharmaceuticals.

The surprising variety of diseases addressed by cannabinoid-based medications will be an ever-expanding boon to humanity. At the same time there will likely be new cannabinoid molecules with unexpected properties synthesized, by pharmaceutical companies and by illicit entrepreneurs who tout them as psychological wonder drugs designed to enhance happiness, or simply as a new high.

The third future direction for marijuana will be in the pantheon of science history next to the apple that legend says led Newton to conceptualize gravity and Alexander Fleming's messy lab bench where bread mold fell on an open petri dish and gave us penicillin. Before we discovered endorphins, we were researching why opium from poppies has such power over pain but can also lead to devastating addiction. A parallel path of discovery followed research into the effects of marijuana. If scientists had not been investigating how marijuana's THC interacts with the brain, we might still have no knowledge of our endocannabinoid system. Because anandamide and 2-AG are not stored in tiny vesicles waiting to be used, they were not as easily discovered as other neurotransmitters. THC was the probe needed to reveal the unknown – the research arrow that hit a previously unseen target. Without knowledge of the endocannabinoid system, new medication development would have been put off further into the future. While foxglove led us to digoxin to strengthen weak hearts, willow bark and leaves led us to aspirin to treat pain, fever, inflammation, and clotting, marijuana will eventually spawn an array of medicines to treat a wide variety of illness. The future will place marijuana next to Newton's apple and Fleming's uncovered petri dish, propelled largely by Raphael Mechoulam's decision to start his career by purifying the active ingredient in hashish confiscated from smugglers by police in Tel Aviv.

And finally, one facet of our relationship to marijuana will not change at all in the future. Experience seekers, especially the young, will continue being attracted to the intriguing high marijuana produces. Use will be temporary, or intermittent, for the vast majority of people who try marijuana. However, despite marijuana's gradual acceptance into the fabric of American society, there will always be individuals whose use will be heavy and regular. The reasons for this will be many, from poor judgment, to self-medication of underlying illness or discomfort, genetic vulnerability to addiction, and mere preference – the same reasons that exist today. There will always be those *hasheeshins* who extol marijuana's virtues even as they appear to others to be abandoning active participation in life or complicating underlying personality or mental disorders. America will no longer be willing to arrest and incarcerate users in a vain effort to prevent such excesses by a few. It is entirely unacceptable to sacrifice sufficient privacy and civil liberties to establish enough police control to stop all addiction. We will continue to accept addiction as collateral damage out of respect for individual liberty to access drugs that the vast majority handle without problem or avoid altogether.

We may hope to change the deeply ingrained bias many have toward marijuana use and many more have toward its addictive use. With the trend toward decriminalization, legalization, and "Treatment, Not Incarceration," much of the world has moved toward a more compassionate approach to addicts. The stumbling block for compassion is often economic and political. Who will pay for treatment? Despite good evidence that money spent on treatment saves future medical costs and is less than what we have spent on criminal justice and incarceration, it currently remains difficult in the U.S. to provide treatment to individuals on a timely basis. Financial constraints will be removed only when the benefits of treatment are seen to rebound on society as a whole and compassion for addicts deepens into true empathy. Compassion says, "I care about you." Empathy

acknowledges, "I could *be* you, but for the grace of beneficent circumstances, or God." Only when we see ourselves in each other, when we have the humility to identify with addicts' difficulty accepting their unwanted limitations, will we find the political will to gladly provide adequate treatment. The political benefit of being seen as hard on addicts is still too great to make the financial investment needed.

As marijuana is gradually granted the same legal and cultural status as alcohol, society will be faced with a question it has long sidestepped. Because alcohol is a beverage, people ignore small amounts of use. People proclaim its benefit as a complement to certain foods without reference to its intoxicating quality. Nor are there any qualms about touting the stimulating effects of a morning cup of coffee. Do people really believe that small amounts of alcohol do not produce small mind-altering amounts of intoxication, usually experienced only as *gemütlichkeit* – pleasant and relaxing sociability? Nonmedical marijuana, on the other hand, is always used for the express purpose of modifying experience. This puts the question front and center whether we think it is acceptable to alter our mind with potentially addictive drugs for recreational and/or social purposes. The law in every state gives adults the right to assess the risks and answer this question for themselves regarding alcohol. Nine U.S. states and two countries have at the time of this book's writing given the same right to adults regarding marijuana. The future in the U.S. may well be predicted by results of the latest Pew survey's reporting 62% of Americans favor marijuana legalization, including 74% of Millennials.[23]

Each person in areas legalizing marijuana now must directly face the existential and practical question of whether they choose to avoid mind-altering drugs except for medical purposes. Do they believe they are better off "facing life on life's terms" without pharmacological assistance, relying only on psychological and spiritual means for recreation, celebration, and dealing with discomfort or boredom? The theologian John Calvin certainly thought so. But, throughout history, social and recreational drug use has generally been a firmly established reality and most recreational/social drug users experience little or no significant harm from occasional use. Many adults feel pleasure and find benefit from the consumption of mood-altering substances such as caffeine, alcohol, or marijuana. They trust themselves to know their limits.

Efforts to legalize marijuana rest on the belief that adults' decisions about use are best left to individuals. Your comfort with granting individuals this level of freedom depends on many things: your commitment to civil liberty, your faith in people's capacity for good judgment, your religion/morality, your politics, and your personal and family history, to name but a few. Those who are more skeptical of others' judgment are more likely to want to restrict individuals' freedom to make their own decisions about drug use. The more we trust most adults to make the same responsible decisions regarding marijuana that they already make with alcohol, the less we have to fear legalization. And those of us in addiction medicine understand that honest science-based education and persistent prevention messages will be needed to reduce the number who exceed their limits with alcohol or marijuana, unintentionally and often unknowingly harming themselves and others. Fortunately, treatment and recovery can help most who cross the line into addiction to cross back over again into sober and productive lives, though some will continue using despite living diminished lives.

Will society develop enough empathy in the future to end the scourge of harshly judging those who fall into excess alcohol or marijuana use? While I personally choose to abstain from marijuana use today, it is not because I consider this a morally superior

stance – merely a personal preference to avoid risking even the very subtle impacts pot can have. At an earlier time I chose differently. Circumstances change and so do choices. I deserved no less respect when I used marijuana recreationally than I do now that I abstain, and neither does anyone who abstains completely, uses occasionally, or daily. These are not moral choices. They are more or less healthy choices and I believe people make more responsible choices when given accurate information, freedom, and respect to choose rather than being treated like infants who need to be controlled. Such restrictions only invite rebellion by some, thereby clouding their ability to choose wisely in their own best interests.

The more we learn about marijuana, the more black and white answers are seen as too simplistic. The only realistic options regarding marijuana policy available at this point are to accept the status quo or to move forward into new territory. Maintaining the status quo is impossible because the world is changing under our very feet. Rejection of enforcement-based public policy strategies is gaining momentum. While moving forward with regulating and taxing marijuana lands us in uncertain and scary new territory, we do not need to recoil from this future and leave it to be shaped only by the most enthusiastic marijuana advocates and the mounting power of Big Marijuana. With scientific understanding as our ally, we *can* exert sufficient political muscle to effectively regulate the marijuana industry and we *can* commit marijuana tax dollars to finally help our most vulnerable youth.

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