THE SCIENCE OF WEED

An Indispensable Guide to Cannabis

GODFREY PEARLSON

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To my wife, Judy, and my daughters, Becky and Lishy, who were cheerleaders for this project

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Foreword

Cannabis is the noisiest plant on earth. Between the divisive politics of legalization, the cyclical giddiness and despair over fortunes made and lost in the "dot.bong bubble," and the steady fearmongering over the plant's supposed dangers, the din grows louder, which makes discerning the fictions from the facts challenging, if not at times impossible.

That's why this book is so valuable. Godfrey Pearlson has managed to turn down the volume while increasing the scrutiny of the science. In doing so, he has produced something that every legislator, policymaker, medical professional, and truth-seeking individual should read. It couldn't be coming at a better time.

The truth is cannabis *is* a confounding plant. Does it induce a state of euphoria or unhappiness? Does it quell anxiety or ramp it up? Does it lessen concentration or intensify focus? The answer to all these questions? It does both depending on the dose, the variety of cannabis, the quantity consumed, how it is administered, and the still-mysterious "tone" of each person's endocannabinoid system. We may blithely dismiss it as a mere weed, but this plant is a complicated chemical factory of over five hundred compounds that combine to produce different effects in different bodies.

In addition to the plant's botanical and chemical complexities, the politics of prohibition over the last decades have made things even more complicated. The largest obstacle to uncovering the science of cannabis is the Schedule I restrictions that US (and international) laws have placed on studying the plant since the 1970s. Long before there were Russian hackers and disinformation specialists, the US government knew that the best way to sow confusion was to limit scientific inquiry and simultaneously foment its own disinformation campaign. Schedule I is the perfect instrument to accomplish this. It states that cannabis has no medical use (despite the multitudes of people who rely on it to treat conditions ranging from epilepsy to pain to PTSD) and creates a tangle of red tape that keeps even the most intrepid American researchers away. This is tragic when you consider how much more we would know about the health benefits of cannabis if investigation had been encouraged rather than impeded for the last half century.

This is not to say we know nothing about the science of cannabis. In fact, as Dr. Raphael Mechoulam, the OG of cannabis chemistry and the man who isolated THC and CBD in 1964, told me, we know quite a bit. A quick scan of PubMed reveals over twenty-one thousand studies, many of which have been conducted by an impressive cadre of dedicated researchers from around the globe. Americans, who at times view the world through a very solipsistic lens, tend to discount these studies because they weren't performed within our hallowed borders. But discoveries about the endocannabinoid system, the endogenous cannabinoids our

brains produce, or the effective medical uses of cannabis come from studies conducted abroad. When viewed as a whole, this body of research provides a multitude of clues about how this plant works. But you have to be willing to look for and piece together those clues.

This is exactly what Pearlson, a professor of psychiatry and neuroscience at Yale University School of Medicine, a doctor, and a principal investigator at NIDA, NIMH, NHTSA and NIAAA, has done. He has combed through years of research, old and new, and evaluated the design and conclusions of hundreds of investigations to determine what science actually tells us (and what it hasn't yet told us) about this plant. This is a long-overdue and impressively coherent sweep of history, botany, epidemiology, and biochemistry, blended with a bit of culture and lore, collected into the one volume you are holding in your hands.

You might expect as much from a dedicated scientific sleuth. But the great surprise about *The Science of Weed* is the writing. Most readers, myself among them, struggle to slog through the numbing jargon of journal articles—they can often be as dry as that old bag of marijuana that was stashed in the garage three years ago and forgotten. Dr. Pearlson is a fine writer with a well-honed sense of humor that adds some sheen to material that could come off as dutifully academic. Even though he takes science seriously, he also makes it enjoyable—no easy feat.

Pearlson's authority is further enhanced by the fact that he is an unapologetic child of the 1960s and doesn't hesitate to share some of his own personal experiences, positive and negative, with the plant.

He describes the Holi festival in India, where entire regions of the country drink bhang lassi (cannabis dissolved in yogurt) in celebration of the god Shiva. With the benefit of cannabis, he has happily communed with nature in the Atlas Mountains of Morocco and come to a more intuitive understanding of the music of Karlheinz Stockhausen and Olivier Messiaen. He also ate far too many pot brownies and suffered the uncomfortable consequences of overmedicating, thus casting doubt on those who claim that there are no negative consequences.

In other words, he has been both pleasantly high and highly spooked by cannabis. This strengthens his observations and makes him a far more credible reporter than other so-called experts who raise all sorts of alarms that have little bearing on reality. This is crucial to cutting down the noise. It wasn't that long ago that institutions, medical journals, and an unquestioning media were frothing about cannabis causing men to grow breasts, or blaming it for leading to heroin addiction or reducing sperm counts. As recently as 2019, a fear-baiting book by Alex Berenson called *Tell Your Children* made headlines by distorting research and falsely claiming that cannabis inevitably leads to psychosis and increased violence. Even when the authors of the original study denounced Berenson's mangled misinterpretation of their findings, the mainstream media continued to repeat the false claims, further obscuring the important questions of how we, as a society, should regulate and police intelligent adult use.

It also enables him to better deconstruct the experience of being high and explain why so many millions around the world turn to cannabis as a relatively

safe way of altering their consciousness. For example, it's definitely true that cannabis temporarily limits thinking to the here and now, but how this is interpreted means everything. Certain cannabis-naive researchers would consider this a "cognitive decrement." But Pearlson understands that these effects are temporary and that intense attention to the here and now can also lead to deep absorption in a task—ask any coder in Silicon Valley about the focus they say cannabis provides in their work. Ditto the way it "distorts" time. In one experiment, subjects who were high were asked to estimate how much time had passed between the sounding of two musical tones. One person responded, "A billion, trillion, quadrillion milliseconds," which is a far more accurate (and poetic) depiction of the gooey way cannabis-time passes than "3.5 seconds." (It also sheds light on why so many musicians say cannabis allows them to feel the space between notes.)

But the motivation or creativity bump that comes from being high is not the point of this book. The point is to gain a deeper understanding of how cannabinoids affect the brain's default mode neural network; and how being under the influence affects motor skills like driving (and the challenges of studying this); and why the relationship between cannabis and psychosis is not causal; and how one plant can treat illnesses as diverse as arthritis, epilepsy, Parkinson's, anorexia in AIDS, IBS, and chronic pain. With this scientific knowledge behind us, we can proceed more sensibly, more calmly, to using this plant to its maximum potential.

That's why I invite you to turn the page and dig in. You may never call it "weed" again.

Joe Dolce, author of *Brave New Weed:*
Adventures into the Uncharted World of Cannabis

THE SCIENCE OF WEED

INTRODUCTION

In 1970, perhaps as a prelude to their subsequent one giant leap for mankind, NASA fired a bunch of frogs into space. The amphibian astronauts were on a one-way mission designed to investigate the effects of weightlessness on the inner ear. Hearing of this event one evening, a regular at the local pub speculated what it might be like for a helpless creature with little sense of self to be blasted at enormous speed into the silent darkness of space. I was the only one at our table who could address that question from personal experience.

Earlier that year, on my 20th birthday I had baked a mini chocolate birthday cake, employing, alongside the usual ingredients, a fat 2.5 g cube of crumbly Lebanese hashish carefully dissolved in Danish butter. I was unfamiliar with the potency of baked cannabis but well acquainted with my sweet tooth, so I ate a generous serving and proceeded to wait. Half an hour and no identifiable effects later, I concluded I must not have consumed enough and finished the entire cake. It tasted surprisingly good.

Forty minutes later, I was seated at the dining-room table chewing a piece of bread when my mouth became extremely dry. “This bread is as dry as a stone,” I said and spat it out. The barely moist bread flew to my plate and rattled like a handful of beach pebbles. I was astonished. Unbeknownst to me at the time, I had just experienced what neuroscientists refer to as synesthesia, a phenomenon where sensations from one sensory system produce signals in another (that is, the ability to taste colors or see music).

Feeling tired, I lay down on my girlfriend’s bed. Within minutes, I had the vivid, unpleasant, and increasingly frightening feeling of being shot from a cannon at supersonic speed and traveling faster than any roller coaster into the blackness of starless space. My ego and sense of self dissolved into the pure sensation of a barely sentient being, devoid of an identifiable physical location. I was accelerating ever faster into the void, terrified by the uncontrollable fragmentation of the familiar “me”—body and mind, my otherwise inseparable companions in life. Now, there was only the elemental, explosive experience of my inner self being hijacked by a malevolent, uncontrollable bat out of hell.

Occasionally, I would become aware of my unpleasant reality, and during those brief moments of quasi lucidity, I was certain I had gone permanently mad. My girlfriend sat by my side and held my hand throughout as she became increasingly anxious. Amid one of my fleeting returns to earth, I asked her how I could break the news of my emergent psychosis to my family and medical-school supervisor. Her brutally honest, albeit practical, response was “If you’ve really lost your mind, I’m not sure I can stay in a relationship with you.” Familiar with Kafka’s *Metamorphosis*, I easily identified her instinct to move away from unpleasant

transformations but was nevertheless saddened by the implied distancing. And then just like that, I was back in interstellar space.

Luckily for me, my sense of self reemerged within a few hours. I regained control of my thoughts and bodily sensations. My previously disparate mind and body rejoined to manifest my physical presence within my current reality. Time ticked at a familiar pace, and I was no longer convinced I'd gone crazy. Instead, I now knew precisely what it felt like to be a helpless creature blasted into outer space, unprepared for the mental and physical toll of the journey.

This experience did not permanently alter my psyche, but it helped cement my career choices and academic focus. I developed a keen interest in cannabis's effects on the brain and body, and chose to pursue a career as a psychiatrist and clinical researcher to further explore these powerful forces. The psychological sequelae of my experience confirmed my prior interest in psychotic disorders, such as schizophrenia, which echoed my transient experience with cannabis. Most importantly, my brief stint as a psychonaut helped me connect and empathize with people who were chronically psychotic, lost in a frightening alternate reality, and unable to navigate home.

This book is about the science of cannabis. In the first part, I examine the origins of the cannabis plant, its chemical structure and composition, and its interactions with humans throughout the centuries and with the internal cannabinoid system of the body. In later sections, I will explore how plant-derived cannabinoids produce the subjective "high" and medicinal effects experienced individually; I'll then move to the plant's collective impact on economics and healthcare, with a focus on how scientific scrutiny has contributed to the contentious debate about marijuana.

I use the terms "cannabis" and "marijuana" interchangeably throughout the book to signify THC-containing chemovars of cannabis, and the word "hemp" when I'm referring to non-THC-bearing plant varieties used primarily for fiber or seed production (although the latter contain CBD).

My apologies if you are a lonely farmer in the Castro Valley who purchased a book titled *The Science of Weed* in hope of learning the latest research advice on eliminating thistles and other pesky weeds from his or her property. This book is not for you. Nevertheless, the thematic threads of "What is science?" and "How can we understand the medicinal properties of marijuana?" are woven throughout the book and will likely interest clinicians and cannabis cultivators alike.

Beginnings

I will rewind events here to relate how I became interested in cannabis, psychosis, and neuroimaging of recreational drugs. The first time I ever encountered cannabis was as a high schooler in 1966. The local British police, in some early precursor of "Just Say No" or DARE, visited our grammar school to lecture on the evils of drugs—that is, every known pharmaceutical compound excluding alcohol and tobacco. Needless to say, questions were not encouraged. Police gospel was that

all recreational substances were indistinguishably bad and equally damaging, if not lethal. To provide concrete examples of this deadly potpourri, law enforcement personnel, as embodied in two large, wearied policemen, passed around illustrative examples of "Satan's manna" contained within a dozen or so thick glass pharmacy jars. One contained a variety of brightly colored pills and capsules, while another displayed tarry dark chunks of hashish that appeared to have been stored in the dusty basement of a Victorian druggist's emporium for the last one hundred years. From our perspective, the police might as well have circulated sampler jars of delectable Willy Wonka ambrosia. To the fascinated audience, this was less of a parade of bad examples and more of a challenge for ingenious young minds. Mischievous schoolboy hands were soon tugging and twisting determinedly, yet inconspicuously, to pry open one or more of the goodie jars. I had my eye on a particular target and, while feigning innocence, gave the *Cannabis indica* vessel my most determined grip and wrench. Alas, it was glued shut tighter than a pharaoh's tomb. Enviously, one bright young lad managed to extract a small handful of pills from another bottle that were later, disappointingly, revealed to be seasickness tablets.

I was introduced to smoking marijuana a few years later at a high-school party and can still vividly recall the scene and sensations. The excitement of the unchaperoned party was palpable; food tasted wonderful; conversation bubbled along delightfully; and I heard Robert Johnson's "Hell Hound on My Trail" in his unforgettably spooky voice for the first time. Whereas alcohol simplified my world and enveloped me in sleepy splendor, cannabis jolted me awake and enhanced my imagination's subtleties, dialing up the inherent humor and friendliness of my familiar universe. I continued using marijuana occasionally in medical school and viewed it as a happy and harmless substance. That is, up until my birthday cake experience. That episode of delirium sparked both a new respect for cannabis (thereafter equivalent to a large generally friendly dog that occasionally bites and needs to be leashed) and a persistent lifelong interest in mind-altering substances. How do they work their magic? What do they tell us about brain function and dysfunction? How can we safely test these effects? During my psychiatry residency, under the mentorship of the inspirational Paul McHugh and Phillip Slavney at Johns Hopkins in the 1970s, I tried to answer these questions by exploring the psychoactive effects of catnip on felines. Perhaps catnip was to house cats what cannabis was to humans—a perfectly reasonable, but as I soon discovered, woefully inaccurate hypothesis.

For my postdoctoral fellowship in 1981, I worked in a research laboratory serendipitously situated next door to Joseph Brady, a pioneer investigator into the behavioral effects of varied abused substances on animals, ranging from rats to rhesus monkeys. A powerful-looking, ruddy-faced man, Joe's research encompassed everything from writing guidelines for ethical research to preparing monkeys for space flight. He loved his work and told anyone who would listen about his most recent project, why he was engaged with it, and what he was discovering. As part of his research portfolio, Joe also collaborated with NASA

and conducted monthlong experiments on groups of human volunteers who lived on a remote research unit, isolated from outside contact. The purpose of these studies was to predict how groups of astronauts might behave on long space voyages in the event of an equipment failure or aeronautical emergency. His animal research, on the other hand, predicted successfully which newly discovered drugs were liable to be abused and ultimately how substance abusers might be treated. I found his work, regardless of species, fascinating.

A couple years later, Joe recruited the behavioral scientist Marian Fischman to join the Hopkins faculty. Marian, who resembled a small, forceful version of Elizabeth Taylor, was a pioneer in safely administering recreational drugs to experienced users in controlled laboratory settings, a nice complement to Joe's animal work. Through persistence and careful preparation, Marian was able to convince safety committees for human subjects that it was important and feasible to conduct qualitative studies on the effects of these drugs in individuals who were already using them recreationally. She reasoned that by systematically studying these experienced users, scientists could assess the effects of these substances on the human body in a naturalistic manner, rather than relying on guesswork or extrapolating effects from laboratory rats. Her research subjects were paid voluntary study participants who were admitted to the hospital or a special research unit for the duration of the study (typically one to two weeks). They could leave the investigation at any time, and if they requested a referral to a substance-use treatment program, they received it. Marian Fischman taught the world much of what we know about the clinical effects of cocaine in humans. Her agile mind probed for details and sought rigor, an asset that made her a valuable, if strict and tough-minded, advisor. Despite an untimely death in her early 60s, Marian nevertheless taught a generation of clinicians how to perform careful, quantitative human drug research, while respecting patient autonomy and minimizing harms. I was lucky to have her as a mentor.

In addition to my burgeoning interest in the neurological effects of substance use, I was equally fascinated by a complementary scientific thread. Several years earlier, Eve Johnstone and Tim Crow had used the newly developed technique of X-ray–computed axial tomography (CAT scanning) to take vivid, precise images of the brains of chronically hospitalized patients with schizophrenia. To the surprise of physicians everywhere, the patient's brains appeared significantly shrunken, with large fluid-filled spaces showing prominently on the images. This finding revolutionized thinking about schizophrenia, reclassifying it as a genuine brain disease with obvious neurological hallmarks, rather than a mysterious behavioral disorder unrelated to the nervous system's anatomy. Inspired by this discovery and its implications for patients with severe mental illness, with the encouragement of Paul McHugh I began talking to radiologists at Johns Hopkins about how I could use neuroimaging to understand what might be affected in the brains of my own patients.

My twin interests in psychosis and abused substances have been intertwined with the use of different neuroimaging techniques for almost 40 years now. I've

been especially interested in how recreational drugs, such as marijuana and alcohol, can alter performance on complex tasks (such as driving a motor vehicle) and their simultaneous effects on the brain. Functional magnetic resonance imaging (fMRI), in particular, has recently emerged as a tool that allows scientists to visualize which brain regions are more metabolically active, or receive more or less blood flow, during a behavioral task. In layman's terms, we are now able to observe which areas of the brain "light up" or "turn down" in response to environmental cues, such as visual or emotional triggers. The problem with assessing complicated behaviors is that there may be so many things going on simultaneously that the entire brain can illuminate like an over-amped Christmas tree. At that point, sorting out which circuit is linked to a specific behavior seems unsolvable. For example, driving either a real car on the highway or a virtual car inside an MRI scanner activates similar brain circuits connected with spatial memory and judgment (such as "I need to take the next exit on the right and keep a safe distance from the car in front,") and holding facts online (such as "The speed limit here is 65 mph," and "It's raining, so my braking distance is longer"). Yet other circuits need to simultaneously coordinate and integrate eye, hand, and foot movements; respond to unexpected events; and focus attention on what's happening on the road and not the squabbling kids in the back seat. Faced with the dauntingly difficult task of disentangling which circuit was doing what, when, in response to which behavior, Vince Calhoun in my laboratory at Hopkins discovered how to apply a novel statistical approach to separate distinct brain circuits that simultaneously switch on or off. The technique, known as independent component analysis, began in the narrow fMRI arena of imaging drunk driving, but it is now one of the most widely used analytic methods in fMRI experiments in the world. Beginning at Hopkins with measuring the effects of different doses of alcohol versus placebo on driving, and some parallel early experiments with cannabis, my laboratory moved to Connecticut in 2002 and began to study in earnest marijuana's effects on complicated behaviors, including driving.

That brings us to the present. Now, as many states ponder legalization of recreational or medical marijuana, cannabis-related issues are unavoidable. In the process of writing this book, I've talked to marijuana law reform advocates and opponents, epidemiologists, geneticists, politicians, dispensary entrepreneurs, psychologists, cannabis consumers, cannabis growery owners, and marijuana botanists. I've interviewed clinicians who treat cannabis-using adolescents entangled in the juvenile justice system, who care for patients with psychosis related to cannabis use, or who run medical marijuana drug trials in the Veterans Affairs (VA) system for patients with PTSD.

The most striking observation I've made is how polarized people's opinions are on marijuana-related issues. This goes hand in hand with the findings of a recent Pew Research Center survey of over five thousand US adults that revealed members of the public struggle to distinguish between factual (able to be confirmed or disconfirmed by objective evidence) and opinion-based (expressing

their views and attitudes) news and views.[1]

I argue that scientific inquiry, by its inherent reliance on objective evidence, can help resolve many of these seemingly stark yes/no, right/wrong arguments. In addition, science can help predict the likely outcome of specific actions, such as legalizing recreational cannabis (e.g., increasing drug dependence or motor vehicle accidents), which can allow for more rational decision-making around these issues. If you've ever used marijuana, thought about using it, wondered why others would use it, or are concerned about how the legalization of cannabis might affect society as a whole, and you think that addressing these questions scientifically might be informative, then I invite you to go on a road trip with me to explore these issues. (But please don't drive stoned.)

Chapter 1

GOOD SCIENCE AND BAD SCIENCE

> Reefers and rhythm seem to be directly connected with the minute electric waves continually generated by the brain surface. When the rhythm of the music synchronizes with the rhythm of the brain waves, the jazz fans experience an almost compulsive urge to move their bodies in sympathy. Dope may help the brain to tune into the rhythm more sharply.
>
> CHAPMAN PINCHER, "Dope: Is There a Link between Dope and Hot Jazz Dancing?," November 28, 1951[1]

> To make matters worse . . . the opposing factions in the cannabis debate often interpret the same scientific evidence differently to suit their own purposes.
>
> LESLIE L. IVERSEN, *The Science of Marijuana*, 2008[2]

It is almost impossible now to plug into the media without being confronted by news about marijuana, or to give it its less contentious name, cannabis. Strong contradictory claims about the drug are made touting opposite conclusions. Cannabis stimulates creativity and has no effect on IQ or conversely causes significant memory loss and lowers IQ. Legalizing cannabis leads to a measurable drop in opioid prescriptions, and fewer opioid-related deaths, or on the other hand an increase in both these measures. Data show purportedly that states legalizing recreational cannabis experience significant increases in arrests for driving while intoxicated and motor vehicle accidents, yet other analyses of the same data sources yield precisely the opposite conclusion. With society making important decisions about cannabis legalization on a state and national level, what information are we to believe? And from which sources? What are the criteria to help us decide who and what to believe? Answering these questions involves bringing science into the debate, so that we can evaluate these competing claims skeptically and help reach our own, hopefully rational, scientifically informed conclusions. But without multiple degrees in toxicology, epidemiology, psychology, ethnobotany, public policy, neuroscience, sociology, and more, what might be a starting point to think intelligently about these issues in an informed way? These types of questions provided the initial push for me to begin writing a popular-science book about cannabis. The idea was to air these debated issues within a scientific framework and in a manner comprehensible to the average person. Popular science is a harsh taskmaster. Lean too far in one direction, and what you write is impenetrable or textbook-dry. But move too far to the other side, and you are at risk of dumbing down the material, oversensationalizing it, or purveying opinions rather than facts.

Which leads immediately to the question, what is science? I'm not just referring to "hard scientists" in white coats, wielding test tubes within white-tiled laboratories or reaching with arcane instruments into particle accelerators—although we will certainly encounter such people in this book. Those individuals will include plant geneticists, botanists, neuroscientists, toxicologists, and chemists. But many more of the scientists we will hear about belong to the so-called soft sciences. These include sociologists, physicians conducting clinical trials, legal policy researchers, epidemiologists, psychologists, and economists. So what do all of these diversely specialized scientists have in common?

Science encompasses both a worldview or manner of thinking about problems and a process of searching and evaluation. Its purpose is to try and explain and ultimately to understand reality—that is, what makes up the universe (including the universe inside our heads) and how it works. In practical terms, science involves using a set of attitudes and practices. In the attitude realm, the key stance is one of skepticism. All of us are inclined to accept conclusions that fit in with our prior prejudices and beliefs. It's a wonderful thing to have our preconceptions confirmed, but we tend to reject contrary evidence without properly examining it. Skepticism involves not reflexively accepting purported facts on faith, even if we happen to like the conclusions drawn, but trying to review the supporting evidence critically whenever possible. In other words, science is based on evidence. It is also helpful to extend the process of weighing facts backward into re-examining whatever evidence led you to your original belief. Another aspect of skepticism is the practice of neither automatically accepting as truthful "what everybody knows," even if it's from a "leading scientist," nor the last thing you read on Facebook posted by Karen. As the saying goes, "Stay open-minded, but not so much that your brain falls out." Taken altogether, science requires using critical-thinking skills.

So, how can we become thoughtful skeptics regarding the information on cannabis that bombards us every day? You, the reader, are no doubt confronted with apparently scientific claims, such as "Scientists show that CBD oil will make your skin smooth and beautiful and cause your wrinkles to disappear," or "Researchers prove that smoking marijuana causes schizophrenia," or "Gateway drug marijuana sparks addiction and violent crime wave in the USA." How can you begin to verify such claims?

Let me suggest the following as a starting point. However apparently strong a statement, the first question to ask oneself is "Is this purported information even scientific to begin with?" What is the quality of the evidence? Many spurious pseudoscientific claims can masquerade as science. Some are easy to identify as such and can be unmasked by simple logic. So, for example, when my friends from the '60s tell me earnestly that, because cannabis is a "natural herb," it must therefore be harmless at worst and is likely good for you, it's easy to refute that argument with examples of equally natural herbs like deadly nightshade, tobacco, and poison ivy. Nonscientific logical chains quickly fall apart when probed. A further aspect of skepticism is to try to unmask any potential ulterior motive of the

person reporting the factoid in question. When such motivation is present, it can often be a clue to underlying poor science or "spin." The skeptical reader should ask him- or herself who exactly published these data, who gathered them, how were they analyzed, and whether the parties involved have an overt or perhaps covert agenda. For example, when a report is released purporting to reveal the supposed good or bad consequences of cannabis legalization ("motor vehicle accidents soar" or "opioid deaths fall dramatically"), it's important to know who paid for the study and any possible motivation to impose a particular spin on the conclusions. Was it a lobbyist for a large liquor-distributing firm anxious that cannabis legalization will cut into their profits, a drug cartel worrying about their own bottom line, a lobbying group that believes that all cannabis is bad under all circumstances, or a state legislature eagerly eyeing a potential source of budget-balancing cannabis tax revenue? Study size is often a key to demonstrating the likely reality of a particular result. Scientists refer to "belief in the law of small numbers." This is the statistical fallacy that something that occurs (often by chance alone) in, for example, a small group of individuals or a small number of coin tosses, scales up directly to the same result in large groups. Chapter 6 will hopefully reinforce the point that "the plural of anecdote is not data." A final aspect of skepticism is one emphasized by Yale professor Dan Kahan, which he calls "science curiosity." People who are science-curious like to challenge themselves by poking around in new evidence, whether or not it contradicts their belief system. If you're a Fox News reader who doesn't mind checking out CNN or the *Washington Post* (or vice versa), then you probably meet some of the criteria for what we might call skeptical curiosity.

My first experience with how science can be "spun" cropped up before my 10th birthday. A local political candidate, part of whose platform was "making our streets safe for children," spoke repeatedly about the fact that several local candy stores (known in the UK as "sweet shops") were selling liquor-filled Italian chocolates. He was instigating a brouhaha based on the supposition that local children would purchase these for purposes of intoxication. Unnamed local "experts" had assured him (he claimed) that this would result in damage to children's brains. As a valiant protector of innocent young lives, he would assuredly root out this scientifically proven menace to our young folk and ban the perfidious Italian chocolates. This controversy piqued our preteen curiosity. Several of us pooled together sufficient funds from our pocket money to buy an overpriced box of said chocolates. Within the center of each confection, we discovered a tiny amount of sickly sweet liquor. Breaking open the entire boxful and decanting off the contents barely filled a teaspoon. We quickly figured out that it would have required eating dozens of boxes of the chocolates to reach a barely perceptible level of intoxication and that therefore the politician was full of it. Collectively, we wrote an indignant letter to the local newspaper pointing this out . . . which was dutifully ignored. This episode made me forever skeptical of substance-related scare tactics, ranging from "LSD will make you stare at the sun and go blind" to "marijuana is a gateway drug that shrinks your brain, damages

your chromosomes, and makes you sterile."

So, now that we're clear on cultivating skepticism to allow us to better understand both ourselves and the world around us, let's move on with our minds open and questioning from scientific attitudes to scientific practices.

The latter includes informal rules, such as first defining the questions you want to ask about some little corner of reality and making one or more predictions about what you expect to find there. Does Halley's Comet whiz by Earth every 75 years? Then we should see it again in 2061. We hunt for predictably reoccurring patterns, and rules and principles that can then be tested experimentally. These practices are an essential part of the activity of science. Questions usually follow logically from an explicitly stated hypothesis about what might be going on. Procedures include carefully defining whatever process you're interested in, the background framework, and the appropriate techniques or technological tools to be used in measuring them. For example, if you want to study 3-inch fish, then don't use a 4-inch mesh net to capture your sample. Scientists strive to be precise and to make fine distinctions. Scientific conversations often invoke metaphorical sharp-edged tools used to dissect facts, from using Occam's razor (simpler explanations are generally better than convoluted ones) to not having axes to grind (see earlier on motivation) so that concise, dispassionate descriptions are favored. For example, not "The mice were angry and thirsty," but rather "On average, the mice fought more with intruders introduced into their cages and consumed 50% more from their water bottles." If your convoluted explanation for an observation involves more than minimal hand-waving and is closer to Occam's chainsaw than his razor, you may have veered way off course, scientifically speaking. If fuzziness is undesirable, so conversely is the false certainty of easy black-and-white answers. That is why scientists generally speak in probabilities. Non-scientists are sometimes impatient with answers that are not definitive, but frequently, key evidence may be lacking, so nuanced judgments are appropriate.

To the possible extent, scientists try to set up experiments that rely on unbiased observation to gather what they believe are the most relevant facts to be collected and then analyze them statistically. Once the researcher has made the observations, she or he wants them to be empirically confirmed by repeating everything at least one more time and obtaining the same result. In other words, are your measurements reliable? As well as reliability, validity is another issue that concerns people performing experiments. If my bathroom scale consistently registers my weight as 120 pounds, I'm flattered but know that the measurement, however reliable, must be invalid. Before concluding that a particular cannabinoid is impairing memory, we first need to determine that it is not just making people extremely drowsy. Humans seem predisposed to explain coherence in nature. Unfortunately, what seems like common sense can easily lead to false interpretations without double-checking everything relevant. Unexpected confounding factors can bollix up the most carefully planned experiments. For example, results of a laboratory study might lead one to conclude that "the mice drank significantly more water after we increased their daily dose of THC." But

before accepting this finding, check that at the same time you did not accidentally change the thermostat setting so that the room was 10° hotter.

Science also asks us to come up with logically consistent predictions based on whatever new hypothesis we have to explain our observations, and it demands that we test our hypothesis over and over again. And the best way to test a hypothesis is to design some experiment that can potentially prove it false, no matter how dear it may be to your little scientist's heart.

Open communication plays a big part in this process, so ideally, every step that scientists go through to reach a particular conclusion should be laid out transparently, not unlike a well-documented recipe. This facilitates sharing data for others to examine. In the process of peer review, other scientists in a specialty area will be able to pick through a manuscript, provide unvarnished feedback and request missing details before allowing publication in reputable scientific journals. They act as gatekeepers to exclude junk science. A positive outcome of this peer review process is that experiments can be recreated, and data can be straightforwardly and independently rechecked by scientists as skeptical as the author. If a particular result is provocative, there are usually doubters who are itching to see whether, if they repeat exactly what the original team did, they will obtain the same results. And if they do, they are likely to be convinced.

Operational definitions of variables should be as clear-cut as possible. Thus, potentially ambiguous terms such as "drug user" should be defined rigorously and transparently. For example, a "cannabis user" could refer to either someone who takes a single bong hit once a year or spends most of their waking existence inhaling large amounts of high-THC concentrates. Or potentially even to someone who consumes CBD gummies devoid of THC content. Scientists who study associations of alcohol with various health outcomes use standard alcohol beverage units that can equate a bottle of beer and a glass of wine. But given the different formulations, strengths, and methods of consumption for cannabis, we run into the vexing question of what constitutes a "standard unit." For example, how do we equate a bong hit of 35% THC Purple Kush with inhaling a sesame-seed-sized morsel of highly concentrated 85% THC and 15% CBD shatter from a dab rig? And how do those stack up against consuming a hash brownie? If you want to show that larger doses of a drug have proportionately more effect on a measure such as memory or pain relief, then you need a reliable and valid measure of dose. Another problematic example is that of "marijuana-impaired drivers." Does this designate individuals pulled over by law enforcement for driving dangerously while simultaneously observed to be smoking cannabis in their car? Or on the other hand, do we include all individuals stopped at a routine police checkpoint who test positively for THC metabolites, even if they last used cannabis several weeks ago? Even the term "cannabis" is used to refer to both pure CBD oil containing no THC, or 1:1 CBD-to-THC concentrate, and to both very high and very low THC-containing marijuana buds. Specificity is always desirable but becomes crucial in cases like these.

Another sensible scientific practice is striving to remain consistent in the way

that we count things. For example, a state may begin to measure cannabis constituents such as THC in the blood of intoxicated drivers and switch to defining intoxication based on the results of blood tests, rather than on roadside behavior as previously. Under those circumstances, it's not possible to directly compare rates of driving under the influence of cannabis before and after the change in measurement practice. The size of the sample and its representativeness of the population as a whole are other important aspects of any study. When conclusions are drawn about drug effects, we want to know that sufficiently large numbers of representative individuals were examined so that the findings are likely generalizable to other populations. Asking 10 of my neighbors whether recreational cannabis should be legalized is less useful than conducting a nationally representative survey of 35,000 adults, although the former it is likely to be much more entertaining.

In addition to the way we count things, *when* we count them may be critical. The economist and mathematician Oskar Morgenstern illustrated this point by noticing that over a 10-year span, the Bulgarian pig population seemed to more than double. But this apparent increase was illusory, based on the nation's change from the traditional Russian Orthodox to the modern Gregorian calendar, causing New Year's Day to shift by two weeks. This dislocation in dates resulted in the first set of pigs being counted *after* Christmas Day (when the number alive and kicking was small, as most had been slaughtered for the holiday), while the second pig census now tallied pigs *prior* to Christmas, when none had yet reached the chopping block (so that their apparent number was much larger). In fact, the overall number of pigs hadn't budged.[3] So, why am I mentioning a faulty 100-year-old Bulgarian swine census? Well, this problematic counting issue applies to the American writer and reporter Alex Berenson's recent claim that marijuana is responsible for rising crime trends in states where cannabis has been legalized. In his controversial book, *Tell Your Children: The Truth About Marijuana, Mental Illness, and Violence*, Berenson states, "Violent crime has also soared in the legalized states since 2013."[4] This claim has received strong rebuttals. In January 2019, a group of criminologists claimed in the *Seattle Times* that they had found "no increase in violent crime that can be directly attributed to marijuana legalization." [5] Beatriz Carlini, a senior research scientist at the University of Washington's Addictions, Drug, and Alcohol Institute (ADAI), commented in the article on the supposed connection drawn between marijuana legalization and crime increases in Washington State (a 17% rise in aggravated assaults between 2013 and 2017). The problem, she points out, is that there was a large one-year decrease immediately prior to 2013, so after that year "the numbers are just creeping back up to where they were before." Thus, picking a starting date of 2013 is stacking the deck, statistically speaking, because crime measurements are likely to trend upward since they are beginning in a trough. Back to the pigs then. Where you pick your starting point to demonstrate a change can be crucial. Otherwise your findings may be hogwash.

To recap a little of what we've learned so far, since any particular hypothesis is

theoretically falsifiable at any point, the job of science is never done, explanations are never complete, and you can never stop metaphorically kicking the tires. Particularly in cases when a scientific finding seems unexpected or provocative, then it needs retesting and confirming in a new population. For example, initial reports suggested that common genetic differences between individuals explained a large proportion of risk for experiencing psychosis after adolescent cannabis use. These data seemed convincing and scientifically plausible, but the original results have been extremely hard to replicate in fresh samples.

Thus, science is an endless process, which I mean in a positive way, rather than how you may have felt in the 10th grade about your last-period chemistry class. Ideally, the theoretical framework you're working with was arrived at rationally and based on solid evidence, is maximally simple and useful, and has an ability to predict events, observations, or circumstances that no one has examined previously.

Scientists are keen on words such as "impartial," "logical," "rational," "unbiased," "neutral," and "objective." Some of the procedures I describe in this book hew to the sort of scientific model I just described. These include such things as measuring cannabinoids and terpenes in chemical laboratories, performing genetic analyses of human or plant DNA, figuring out what wavelengths of light cause cannabis plants to flower, and conducting clinical drug trials of cannabinoid compounds. Other parts of the book venture much more into social sciences, where we are examining things like subjective mental states, and people's intentions, feelings, and thoughts. Chapters that examine what it feels like to be stoned, or why people tend to use recreational drugs in the ways that they do, fall more into this second category.

Human behavior does not obey rigid laws of nature in the same way as subatomic particles in an accelerator do. Causation for our behaviors and consequences is often hard to establish clearly, and the tight, rigorously controlled experimentation possible in the world of chemicals, and even laboratory rats, is never feasible when it comes to people. For example, in an animal laboratory we can administer precise doses of THC or placebo to adolescent mice under carefully controlled conditions and track their subsequent behavior as they make their way slowly and dreamily around tiny mazes. We can then kill them and measure precisely their brain chemistry and structure. However, no scientist in their right mind would ever propose identifying all the 15-year-olds in a large city and randomly assigning half of them to smoke cannabis containing a precise amount of THC every day for 10 years, while giving the other 50% a similar placebo, in order to document how many people in each group developed psychosis. And even if we were to perform such an ethically blighted study, many of the teens would inevitably engage in behaviors that would thwart our would-be experiment, bless their hearts. These might include drinking various quantities of alcohol, using their own cannabis supply in addition to or instead of what we assigned them, dropping out of the study, not answering our survey questions honestly, or using magic mushrooms immediately before answering them. Human beings, in

other words, are refreshingly ornery and complex to study.

So, we might ask, is the type of social science that reports on noncontrolled circumstances really science at all? Philosophers of science regularly engage in amusing spats while debating these types of questions. Maybe the best we can do under such circumstances is to apply whatever feasible elements of scientific logic and strategy that we can to the world of people and to gather as much worthwhile information as possible. For example, it is often practicable for researchers to make careful observations of events occurring in nature. They can obtain parental consent (and the child's assent) to follow a representative community sample of a thousand 10-year-olds every year for 10 years, before the children have ever used alcohol or recreational drugs, and ask them to complete IQ tests and fill out confidential surveys about their drug use. Then they can measure relevant differences among groups with different patterns of subsequent substance use. These latter types of observational studies do not intervene, only track and report carefully what's already occurring.

Humans differ from laboratory rats in many other ways. To make experimental results standardized, laboratory rats are essentially clones, or at least one rat differs minimally from another. Humans differ from laboratory rats in the massively scaled-up complexity of their brains and the substantial differences among most individuals. Furthermore, humans and rodents differ in many aspects of basic physiology. Experimental drugs that produce dramatic therapeutic responses in rats and mice are mostly ineffective in humans. The account @justsaysinmice on X, formerly Twitter, captures funny (if sometimes alarming) examples of this by reposting extravagant science claims that inappropriately extrapolate to humans from rodents with the headline "IN MICE."

Finally, the science hymnbook frequently invokes the refrain, "Correlation does not imply causation." Thus, if A happens, followed by B occurring, this does not automatically mean that A caused B. For example, in the summer months, ice-cream sales and cases of drowning both climb in tandem day by day. This doesn't lead to frantic calls to limit ice-cream sales, because the average person intuits that both occurrences are due to the daily weather. Similarly, if adolescents who smoke cannabis have lower IQ scores than their non-cannabis-smoking peers, then this cognitive difference may be due to environmental factors that have been demonstrated to impact IQ (for example, lack of parental supervision, socioeconomic factors, attending different schools) and that might explain both relevant facts about IQ and a tendency to smoke cannabis.[6,7]

Thus, cannabis use didn't lead directly to the IQ difference, but the same environmental factors explain why both of them occurred. To disentangle this situation, we might want to know whether IQ scores were lower in the cannabis users before they even began using the drug. We could assess whether individuals who smoked more cannabis had significantly lower IQs than those smoking small amounts, so that higher drug doses were associated with larger effects on IQ. Many of these points are relevant to the various case examples that we will discuss in the remainder of this chapter.

Good science, bad science, and how scientific data can be reframed

In writing this book, I would like to help readers reexamine not only what they think about issues including cannabis use and cannabis legalization but more importantly to continue weighing and examining related future questions for themselves, based on their cultivation of logical and skeptical aspects of scientific thinking. With those considerations in mind, let's consider four separate cannabis-related science reports that illustrate different points on a conceptual continuum of scientific quality, plus the case of a recently published book.

Case study number one, from NotAllowedTo.com, is headlined "Marijuana in Space—NASA Discovers THC on Meteorite Fragment": "Astrophysicists from the University of Hawaii have discovered Tetrahydrocannabinol (THC) on a meteorite found in the Nevada desert in 2010. . . . Tetrahydrocannabivarin (THCV) were [*sic*] also found in a meteorite fragment in 2009 by a research team from the University of Mexico but the findings were dismissed at the time because of the 'controversial nature of the discovery.' " The article incudes a quote from astrophysicist James Hun of the University of Hawaii: "If chemical substances, that change brain functions and result in alterations in perception, mood, or consciousness in humans, find their origin in outer space, what role then has [*sic*] cometary impacts played on the human species? . . . This discovery ultimately leaves us with more questions than answers. . . . It gives a whole new meaning to the term getting high." [8]

This story has legs. I have been asked about these "findings" by students several times, and the story has been extensively republished elsewhere. So how do we judge its veracity? First of all, the source, NotAllowedTo.com, is not a peer-reviewed scientific journal but the Internet equivalent of a supermarket tabloid. One representative headline is "Man Who Died of Coronavirus Miraculously Resurrects Three Days Later" [9] The THC meteorite story has been shared hundreds of thousands of times, so it has proved to be effective clickbait, garnering traffic for the website and therefore handy for their advertisers. Flouting the dictum "Extraordinary claims require extraordinary evidence," this scientific claim, unfortunately, was advanced with no valid supporting evidence at all. For example, the astrophysicist whose name is cited as the source doesn't check out on the University of Hawaii's astrophysics faculty list, and the analytic method by which the THC was identified is never mentioned. Conclusion: not science but obvious fake news. Scores an A for chutzpah, F for scientific content.[10]

Case study number two derives from an article published in the *South African Journal of Science* in 2001 by Francis Thackeray and colleagues. The gist is that clay tobacco-pipe fragments from Shakespeare's garden tested positive for THC metabolites, and similar fragments from the same English town tested positive for traces of cocaine and several other recreational drugs, in addition to the expected nicotine. The authors' conclusion was that Shakespeare smoked cannabis for inspiration.[11] Thackeray's team of collaborating scientists employed the analysis technology of gas chromatography–mass spectrometry (GC-MS; explained later in study number four), whose necessary equipment resided in a South African

narcotics crime laboratory. This technique uses electrically charged molecules to develop a very specific fingerprint that can identify chemical substances with 100% specificity. Its many uses include explosives and drug detection, and coincidentally planetary probes to screen, for example, samples from the Martian surface. So theoretically it could have been used to examine the Nevada meteorite, had it existed, in case study number one.

The tobacco-pipe specimens were excavated from the site of Shakespeare's garden, from a home that he owned in later life, from his birthplace, and from locations elsewhere in the environs of his hometown of Stratford-upon-Avon. There was no evidence that any of the pipe fragments belonged to Shakespeare himself, but only that they were excavated from places in and around where he lived. Evidence for the presence of THC or related chemicals was less than convincing. The 2001 study stated that "unequivocal evidence for cannabis has not been obtained." The researchers detected GC-MS signals, hinting at cannabis-related compounds but in quantities insufficient for proof.[12] Essentially the same findings were reanimated a decade and a half later, discussed in an editorial[13] and in newspaper articles written by and about Thackeray and his findings.[14,15] So the story is still alive and appears regularly on the Internet. The idea that the immortal Bard, who invented the word "addiction" (*Othello*), was a druggie is apparently too entertaining to let go.

When I discussed the "was Shakespeare a stoner" thread with my laboratory group at one of our weekly marijuana science meetings, it elicited an immediate shower of cannabis-influenced alternative titles for Shakespeare's plays, including *As You Light It*, *Much Ado about Puffin'*, *Titus Hydroponicus*, *The Hempest*, *The Taming of the Shroom*, and *Henry and the "Eighth."* But the claim seemed to have sufficient plausibility to avoid dismissing it out of hand, so let's review the science with a skeptical eye.

Since Thackeray's chemical-analysis method of GC-MS yielded equivocal data, he sought additional support for his hypothesis not from the world of science but from that of literature. He bolstered his claim with Shakespearean quotes. For example, Shakespeare's "Sonnet 76" refers to "a noted weed" ("Why write I still all one, ever the same, / And keep invention in a noted weed"), and later in the same sonnet, he writes of an aversion to "compounds strange." The consensus of Shakespeare scholars is that "weed" in this context is synonymous with clothing, not drugs, as in a "widow's weeds." Use of the slang term "weed" for drug cannabis first occurred around 1910 in the United States. King James I's contemporary *Counterblaste to Tobacco* refers to the latter as "herbe," not weed, a more likely contemporary term for a drug plant. There is also a lack of plausibility in multiple aspects of Thackeray's account. Nobody knows who owned the pipes from which the fragments derived. There's no evidence that Shakespeare possessed or smoked them. Where might the cannabis purportedly smoked in them have originated? While non-drug hemp has been grown in the United Kingdom since the Viking period for rope and sail making, drug cannabis as an intoxicant didn't reach England until the 1830s from India. If Shakespeare was indeed

smoking cannabis, he failed to record this other than in one ambiguous line in a single sonnet. And drug cannabis was not illegal in Shakespeare's time (albeit unknown), so he would have had no disincentive to describing his use of it. Similar skepticism applies to claims that traces of cocaine were found in some of the pipe fragments analyzed. Cocaine hadn't yet reached England from South America in the Elizabethan era. Smoking or vaporizing coca leaves is pointless: it yields no psychoactivity, because the concentrations of active drug alkaloids in the leaf are extremely low. Also, smoking would destroy by combustion any that were present rather than releasing any intoxicants. While coca leaves can be chewed or brewed in tea to produce mild stimulation, smoking the plant to get high never developed in traditional culture (unlike marijuana or tobacco, for example). Using modern chemical techniques unavailable in Elizabethan England, one can now extract highly concentrated forms of the cocaine alkaloid and process them into smokable product such as "crack," but this was unknown until four hundred years post-Shakespeare. So the supposed cocaine traces remain tough to explain.

What additional evidence might make Thackeray's initial claim more believable? One strategy might be to test other pottery such as cookware from the same garden as a control, to see if this also yielded positive results for traces of cannabis, cocaine, and the other drugs claimed to have been detected by GC-MS. If any type of Elizabethan pottery revealed the same chemical signatures, that would make the specific findings in the pipe fragments seem less plausible. One could also test contemporary miner's clay tobacco pipes from other locations in the United Kingdom. Working-class men from the same time period would be most unlikely to have used any of these intoxicating substances, so showing their tobacco pipes bore no drug traces would be important as a negative control. Unlike the recent use of GC-MS by archaeologists to reveal chemical relatives of THC in Chinese gravesites, the South African instrument seems to have stretched technology to its limits 25 years ago, using equipment that was designed for large drug specimens confiscated by police around the year 2000.

The overall conclusion one draws from this story is that despite a startling initial claim, no substantive new supportive evidence has emerged.[16] This publication receives strong ratings as a great after-dinner speaker's story but is not strong science; and without further corroborating evidence, it is low in plausibility. But unlike the first story, it actually is science.

Case study number three. The newborn nursery at UNC Hospitals began using a revised drug-testing protocol in February 2011 to screen infants who may have been exposed to abused substances during their mothers' pregnancies. Urine samples for testing were collected using various procedures but usually by swabbing or squeezing the inside of the infants' diapers. Alert nurses reported that the number of positive screens for THC in the infants had shot up to nearly 20% since the new protocol was instituted. Were they facing an epidemic of cannabis-abusing mothers? If so, then this had potentially serious consequences in terms of mothers being charged with child abuse or social services being called in, or even infants being removed from their parents. (As one article has pointed out,[17] drug

testing is performed much more often on children of “at risk” mothers who are single, poor women of color.) A team of laboratory scientists, physicians, social workers, and nurses led by Catherine Hammett-Stabler, a UNC professor of pathology and laboratory medicine, figured out that a baby-wash product was causing false-positive readings on the cannabinoid/THC immunoassay. More precise testing with mass spectrometry and other laboratory techniques on the positive infant urines came back with uniformly negative results on the same specimens that had previously tested positive on the nursery’s new commercial drug-testing screen. The team next added small amounts of various baby-wash products to clean urines and found that many specimens then came up positive on the commercial baby-pee screening test.[18]

Bottom line: in this study, thoughtful, hypothesis-guided detective work, aided by properly used laboratory techniques, curtailed a hospital from leaping to false conclusions.

Case study number four concerns the recent report from Meng Ren and colleagues at the Institute of Vertebrate Paleontology and Paleoanthropology at Beijing’s Chinese Academy of Sciences.[19] This group examined the funeral braziers and cannabis-plant specimens from a 2,500-year-old cemetery in Northwestern China. As in the Thackeray study, the analytical method used to identify cannabinoids was GC-MS.

Whereas the experimental details are relatively skimpy in the Thackeray report, the Ren study provides much more comprehensive information on how their analysis was carried out, as well as a lengthy supplement showing the specific chromatograms (images created by the GC-MS analysis) from the charred wood and burnt stone in each brazier, plus a photograph of an easily identifiable cannabis plant taken from one of the tombs. We’ll discuss this study more robustly in Chapter 3, but suffice it to say that this degree of detail makes the results not only easy to understand but also more believable because of the high degree of specificity. Whereas the first study detected mass-to-charge ratios of compounds that suggested cannabinoids, but “not in quantities sufficient for proof,” the second conclusively found measurable quantities of cannabinol (the cannabinoid that THC eventually decays into), along with CBD. Thus, the Ren study meets criteria for high-quality, scientifically rigorous research.

The final case example is not a study but a recently published book: Alex Berenson’s *Tell Your Children*.[4]

When I encountered Berenson’s claim in *Tell Your Children* that marijuana use is directly responsible for an unprecedented epidemic of psychosis and violence in the US, my dubiousness index went up several notches. Berenson is a former *New York Times* reporter who has written clearly and thoughtfully on a variety of topics, toured Iraq twice to cover the war, and subsequently retired from journalism to write 10 or more successful spy novels. More recently, he’s allied himself with right-wing American media and positioned himself as a skeptic regarding the seriousness of COVID-19, and claimed that the COVID vaccine was both ineffective and dangerous. *Tell Your Children*’s central argument is that

“marijuana causes psychosis. Psychosis causes violence. The obvious implication is that marijuana causes violence.” He writes, “The black tide of psychosis and the red tide of violence are rising together on a green wave, slow and steady and certain.” [4]

I believe that it’s worth devoting some time to discussing his published arguments critically, because Berenson states that he gathered large amounts of evidence and interviewed “some of the world’s foremost experts on marijuana and mental illness” to reach some controversial and, in the opinion of many scientists, misleading conclusions.

Let’s take a look at the evidence behind some of Berenson’s claims and try to put the data in perspective. If we dived into the existing published scientific literature to try and address these issues ourselves, what would we discover?

First, is cannabis use associated with violence? Cannabis use can certainly make people disinhibited and impair their cognition, so the idea that there might be some increased risk of violence in the context of cannabis use is not entirely far-fetched. The drug’s propensity for unleashing violence does not seem to be particularly marked however. For example, early investigations concluded that “the consensus is that marijuana does not precipitate violence in the majority of those using it sporadically or chronically.” [20] More recent reviews are clearer that a moderate, rather than powerful, statistical relationship exists between cannabis use and violent behavior, and they stress that such links are strictly correlational in nature.[21,22] In other words there is some association, albeit not a strong one, and it’s unclear what is causing what. Risks for violence in cannabis users seem to be rather limited to some individuals with mental illness, cross-sectionally so for PTSD and longitudinally for psychosis spectrum disorders. “However the presence of uncontrolled confounding factors in the majority of included studies precludes any causal conclusions.” [23]

Delving a little further into this question reveals complexities. Mechanisms of how cannabis use might boost risk for violent behavior remain unclear.[24] The situation is muddied further by the fact that legalization of recreational cannabis leads to declines in general criminality and violence as illicit underground drug dealing decreases. Another wrinkle is that youngsters who exhibit more aggressive tendencies between ages 10 to 16 are more likely to use cannabis at ages 16 to 18.[24] This likely argues for any association between cannabis and violent behavior being bi-directional. In other words, potentially violent kids are more likely to go on to later use cannabis, in addition to teenagers who use cannabis being somewhat more likely to exhibit violent behavior.

A related issue is whether schizophrenia specifically, or psychosis more generally, is associated with the risk of violence toward others. Research studies that examined 40 years’ worth of the published literature on risks of interpersonal violence and violent criminality in schizophrenia patients found substantial heterogeneity in reports. Which is a polite way of saying that the data are far from reaching any firm conclusion. Studies agreed that patients with psychosis in general (compared to those without mental disorders) had an increased likelihood

of violence that ranged anywhere from no increase at all to seven times the odds. People with psychotic illnesses who were also substance users boosted their odds of violence by about four times, but this was not a specific cannabis effect.[25]

Another important question is what are the relative risks of cannabis use being associated with violence as opposed to those of alcohol use? One recent meta-analysis of almost three hundred thousand adolescents and young adults calculated the odds ratio for youth cannabis use being associated with the risk of perpetrating physical violence to be just greater than doubled.[22] To put this in perspective, a Swedish study of violent offenders recruited from a prison evaluation unit examined the role of alcohol and drugs in triggering criminal violence. It discovered an approximately 13-fold increase in violent behavior within 24 hours of alcohol consumption.[26] Although the two studies are not exactly comparable, as they used different methodologic approaches, the bottom-line numbers do help put cannabis-related risks in perspective. And here the literature is not in dispute: alcohol as a recreational drug is many times more likely to result in violent behavior than is cannabis.[27]

Finally, are schizophrenia rates rising because of the legalization of cannabis or for any other reason? We know that THC in cannabis, particularly when used frequently and in high concentrations in adolescence, can predispose to psychotic illnesses. (Although CBD and other constituents of the cannabis plant can be used to treat schizophrenia.) The 2017 National Academies[28] report summarized that "cannabis use is likely to increase the risk of developing schizophrenia and other psychoses." This conclusion is supported by some evidence of increasing rates of schizophrenia in Europe,[29,30] although not in the US, where accurate reliable tracking of psychosis rates is not available.[31] Evidence from Scandinavia suggests that these increases may be attributable to increasing cannabis use.[29] However, as pointed out by David Nutt, the number of cases of schizophrenia in the UK has not risen dramatically. If rates had surged, then this would have been detected. For example, in the United Kingdom in the 1990s, alcohol consumption rose by 50%, accompanied by an obvious and dramatic 50% increase in deaths from chronic alcoholic liver disease.[32] The best, most recent estimate is that cannabis may be responsible for 20% of cases of schizophrenia among young males age 16 to 25.[33] That age range is the peak for new cases of the illness in men, who develop schizophrenia more often than do women. And again, to put things in perspective, the base rate for total schizophrenia cases in the population is 1 in 100. Another subtlety is that both substance use (including cannabis) and psychotic illnesses (including schizophrenia) run in families, and each has a genetic basis. Several studies now suggest that some of the same gene variants predispose to both conditions.[34,35] Geneticists refer to such circumstances as "confounding." The phrase implies that the genetic risk for one disorder influences the other, so that they are intertwined, or confounded. Thus one condition cannot be said to lead directly to the other.

Pulling all this information together, we can conclude that there is some kernel of

truth in Berenson's assertions, with the facts supporting a greatly nuanced, considerably less dramatic version of his claims. To be fair, this is a rapidly moving field, and not all the key evidence was available to Berenson at the time of writing his book on cannabis. Evidence does not suggest to me that cannabis is either inherently or, through its admitted relationship to some cases of psychosis, a major risk for violent behavior to anything like the extent that he portrays it, and this aspect of Berenson's argument in particular is greatly overemphasized. So, it's important to understand how scientific findings can be spun in support of a particular agenda, as I believe they are in his book. More explicitly, I would further assert that many of the arguments employed by Berenson are skewed. But I don't want to devote an entire chapter to an extended book review, so I'll tackle a single issue here: the question of whether, as Berenson suggests, cannabis use is leading to a schizophrenia epidemic.

Thus, my problem with his book is twofold: my first concern is that readers will be unnecessarily panicked by Berenson's magnification of cannabis's harms. My second worry is in some sense the opposite: that people will discount his alarmism and invalid arguments and therefore dismiss the entirety of Berenson's book, including his genuine assertions. These latter include, for example, the data that there is an increased risk of psychosis associated with the drug (albeit a much smaller one than he posits[36]) and the notion that part of the reason for reduced perception of cannabis's harm includes pressure from dubious commercial interests. But when, as is the case here, a case is significantly overstated and claims run ahead of the evidence, it's easy for readers to categorize the author as the boy who cried wolf, so that the valid points are tossed out with the hype. The book has been editorialized by Berenson himself,[37,38] and reviewed multiple times both favorably[39–43] and critically,[17,44–53] and debated in a roundtable.[54] I acknowledge a debt to these authors, debate participants, and others[55,56] for first raising many of the issues I summarize further. So let's examine Berenson's major points regarding schizophrenia.

Does marijuana cause psychosis?

Berenson makes much of the statement in the 2017 National Academies[28] report that "cannabis use is likely to increase the risk of developing schizophrenia and other psychoses; the higher the use, the greater risk." But he pushes this too far in concluding that cannabis smoking is directly responsible for very large numbers of new cases of schizophrenia that would not otherwise arise. During the Marshall Project's debate on the dangers of cannabis,[54] Berenson stated, "Marijuana causes psychosis. This is an established medical fact, not open to debate. . . . The mainstream literature and the physician-scientists who have done the most work on the issue also believe it is responsible for some cases of schizophrenia that otherwise would not have occurred—that is to say, that it can cause schizophrenia, especially when used regularly to heavily by adolescents." But this relationship is far more nuanced than Berenson's stark statement that cannabis causes

schizophrenia. In discussing schizophrenia risk, the NAS report was much more balanced than Berenson's summary. It stated that the relationship between marijuana and psychosis was "multi-directional and complex," and that many other non-cannabis related factors are involved in its genesis, including genetic background and family history.

This issue was clarified by pharmacologist Ziva Cooper, an expert on effects of cannabis and cannabinoids. She is the research director of UCLA's Cannabis Research Initiative and one of the authors of the National Academies 2017 report that summarized what was then known about the relationship between cannabis and psychosis.[28] Dr. Cooper posted the following on X:

> In response to the recent *New York Times* editorial on cannabis and as a committee member on the NASEM cannabis and cannabinoid report, we did NOT conclude that cannabis causes schizophrenia. We found 1) an association between cannabis use and schizophrenia and 2) an association between cannabis use and improved cognitive outcomes in individuals with psychotic disorders (not mentioned in the editorial). Since the report, we now know that genetic risk for schizophrenia predicts cannabis use, shedding some light on the potential direction of the association between cannabis use and schizophrenia. We also now know that under placebo-controlled conditions, cannabidiol (CBD) improves outcomes in patients with schizophrenia when given as an adjunct med, showing that cannabinoids (not necessarily cannabis) improve symptoms.[57]

Ziva Cooper's comment regarding genetic risk refers to findings from a group of Dutch investigators who in 2018 examined the heritability of cannabis use (which is known to run in families).[34] They found 21 genetic variants in the form of commonly occurring alterations in a single DNA coding "letter," which explained 11% of the variance in this heritability, actually a very high proportion in these sorts of analyses. They then performed a complex analysis that showed evidence for a positive influence of schizophrenia risk on cannabis use. In other words, this finding provides some evidence that genetic risk for schizophrenia may influence marijuana use, so that the causal path is not necessarily one leading directly from cannabis to schizophrenia. In short, the two are confounded. Although an often-cited study from New Zealand showed evidence of schizophrenia following youthful cannabis use,[58] the more recent Di Forti paper[59] did not. Marta Di Forti found that while cannabis potency and frequency of use were strong risk factors for the development of psychotic illness, age of first use was not. So this portion of the story remains somewhat unresolved for now. To summarize, as H. L. Mencken said: "For every complex problem, there is an answer that is clear, simple, and wrong." Berenson's assertions, I believe, are not so much wrong as overly simplified at the expense of ignoring rather subtle and complex disease risks and also exaggerated or amplified significantly more than the existing evidence supports.

Another major point in the "marijuana causes psychosis" argument is that acute anxiety and paranoia after using the drug plus delirium and transient psychotic events are very different from cases of schizophrenia. The latter illness characteristically involves persisting positive symptoms (like hallucinations) and disabling negative symptoms (like apathy), plus a deterioration in life course. In Berenson's book however, "psychosis" and "schizophrenia" are not consistently

distinguished; acute versus chronic psychosis-like symptoms are not always taken into account; and one set of terms tends to elide with the other. During the Marshall debate, Mark A. R. Kleiman, professor of public policy at NYU, alluded to this.

> In addition to wanting to know what sort of "psychosis" cannabis might cause, it's sensible [to] want to know how often these bad things happen: both what fraction of psychosis is attributable to cannabis and what the probability is that any given pattern of cannabis use will lead to psychosis [or schizophrenia] . . . however defined. . . . I think the problem is more the difference in professional practice between journalism and science.[54]

What is the evidence that rates of schizophrenia are rising because of marijuana use? Let's try and parse that statement. Outside of isolated testimony in his book from various emergency-room physicians, there are no nationwide data to suggest there is an upswell in psychosis incidence in the United States, as Berenson claims. Nationwide incidence rates of serious mental illness are hard to track accurately without systematic, multi-city household surveys such as the Epidemiological Catchment Area study.[60] There is no mandated reporting for psychotic illnesses in the US as is required, for example, in newly diagnosed cases of tuberculosis or HIV. But Berenson's statements regarding 18- to 25-year-olds seem inconsistent with his other claim elsewhere in his book that many cases of supposedly cannabis-caused psychotic illness are actually appearing in marijuana users who are *outside* of the standard age of risk, in older previously stable individuals.

Finally, as an investigator who is personally administering typical doses of cannabis to volunteers in four separate federally funded research studies, among hundreds of doses provided to our subjects that they have rated as "typical of what I would use by myself or with friends," I have seen zero instances of psychotic symptoms. This is not at all to claim that such events never occur but that they are nowhere as common as implied in Berenson's book.

Berenson says of those who deny the connection between marijuana, psychosis, and rising violent crime rates that "the tricks can be hard to find—and journalists who are almost never trained in science or statistical analysis often parrot the results unskeptically, especially when the findings confirm their own biases toward ideology or sensationalism. Once car accidents and violent crime are involved, the results can be deadly." I think this criticism could equally well be reflected back on his own arguments. This point was emphasized in a February 2019 "Letter from Scholars and Clinicians Who Oppose Junk Science about Marijuana." The letter states that "the vast majority of people who use marijuana do not develop psychosis and schizophrenia, nor do they engage in violence, thus making Berenson's claim far-reaching and exaggerated." [56] A further point is Berenson's dismissal of the claims of David Nutt, a British professor of neuropsychopharmacology whom I alluded to a little earlier. Dr. Nutt has researched extensively and written cogently on diverse drug-related topics as well as publishing with other distinguished researchers (see Chapter 7) on the topic of how to rank drug-related harms. Berenson dismisses Nutt's work as the product of

some slightly loopy fringe scientist. But this brushing aside of Nutt's work stems perhaps more from his ranking of cannabis significantly below that of alcohol in terms of its score on an empirically derived relative harm index—an example of Berenson's cherry-picking.

Science is a consistent, organized, and ruled-based enterprise. Through a process of gathering, measuring, sorting through, and analyzing observations, it accumulates knowledge. In turn, that is used to construct testable, potentially falsifiable hypotheses about the objects and events in our universe. As well as the practices of science that help us to decide whether a particular study has incorporated the procedures and safeguards that meet the criteria for believable science, cultivating a skeptical scientific *attitude* is essential to help us think clearly through all scientific endeavors (including of course cannabis-related issues).

In this chapter, I have provided a few examples of what I consider good- and poor-quality science in action. The hope is that these illustrate how mistaken, biased, or incorrect conclusions can be minimized. To summarize a few key points, helpful principles to keep us on the right path include encouraging the practices of healthy skepticism and curiosity in sorting through and dealing with the flood of often contradictory information that is available to all of us on the Internet. If an important aim is to help all of us put information in perspective, then striving to avoid bias, figuring out whether individuals making claims are clear about how their results were obtained, and determining who they represent are all useful practices. Also helpful in reading beyond the headlines is to look out for whether key data are being counted consistently and whether correlation is being confused with causation.

Such modes of approaching problems help us avoid the extremes of cannabis boosterism on one side of the spectrum and alarmism on the other. This then enables, for example, more rational planning of harm-reduction policies and dispassionate comparisons of marijuana-associated risks to those of other widely used recreational drugs.

Chapter 2

HOLI

Alles, was ich erzähle, ist erfunden.
Einiges davon habe ich erlebt.
Manches von dem, was ich erlebt habe, hat stattgefunden.

[Everything I narrate is invented. Some of it I actually experienced. Some of what I experienced actually happened.]

MATTHIAS BRANDT, *Raumpatrouille*, 2018[1]

How can science (as I defined it earlier) help us think rationally about cannabis in a way that can guide public policy? To set up many of the key issues that we will revisit in different parts of this book, I'd like to start with a narrative that raises questions many people have about cannabis. These topics include "What are typical motivations for people to use cannabis?"; "What methods do people use to get high?"; "What are typical drug effects?"; "Why do different individuals have such different experiences after cannabis use?"; "Why do some people have long- or short-term problems after using the drug and not others?"; and finally "What are some of the issues society will need to cope with, and what key decisions are to be made, if cannabis is legalized at a federal level in the US?" One way to begin considering these issues is to start with a story that helps lead us through them, in part by understanding the motives and experiences of ordinary people using the drug. The remainder of the book then addresses those major topics.

OK *Jeopardy!* fans—here's a clue for you. "This city is associated with Day-Glo colors, music, dancing, and large-scale public marijuana consumption." Any guesses? If you said, "What is Portland, Oregon?" think again: the correct question is "What is Varanasi?" Cannabis-wise, this North Indian city is a couple of thousand years ahead of us in the United States, so presumably they have much to teach us. Let's dive in and explore. Oven-like in the summer, but surprisingly chilly for half the year, Varanasi, previously known as Benares, is one of Hinduism's seven holy cities, famous for its 88 sets of slabbed stone steps (sufficient for more than seven 12-step programs). Some of these flights of stairs (known as "ghats") are spectacularly beautiful. All lead down to the Ganges River, on whose north bank the city was constructed. Visitors cruising by the steps in brightly colored boats observe bathers immersing themselves in the river that is sacred to Hindus. Their cremation ceremonies, along with meditative and religious rituals including evening fire worship, all unfold on the ghats. Although many

Hindus believe that dying in this holy city leads to Nirvana, the state of bliss we will focus on here is an earthly one, associated with the large amounts of cannabis that have been consumed in Varanasi during the annual festival of Holi since its beginning at least seventeen thousand years ago. The plant is called *Cannabis indica* due to its ceremonial use in India. For Varanasi in particular, that use is ancient and thus provides a useful window into the drug.

Given the many religious and historical legends linked with Varanasi and Holi, trust me for a minute to take you figuratively by the hand and lead you on a mini-pilgrimage down the steps of myth. One of the 88 ghats is intimately associated with the Hindu deity Lord Shiva, regarded by some as the supreme god in the Hindu pantheon. Shiva is not only linked in legend with Varanasi, but the city was dedicated to him sometime in the 8th century. Most relevant for us, among the pantheon of deities, Shiva is traditionally depicted as enjoying the many forms of cannabis, including bhang—ground cannabis that is blended into drinks or sweetmeats. Legend has it that Shiva dwells with his family and followers in a distant Himalayan peak, where he can only be reached by crossing a burning ghat and jettisoning one's mortal body. Using cannabis is a traditional means of unity with the spiritual world and communing with Shiva, aided by his favored drug, through enhanced meditation.

Several varieties of cannabis are consumed most often during the Hindu celebration of Holi. This festival of bright colors, play and laughter, thanksgiving and springtime, is celebrated through much of India and Nepal. It's useful to distinguish among the Indian terms for cannabis used here. "Ganja" is the Sanskrit word for dried cannabis buds and leaves, while "charas" is cannabis resin (handmade hashish). "Bhang" is marijuana paste made from cannabis leaves and stems. Bhang is added to edibles, principally bhang lassi and bhang thandai. Ganja and charas are smoked, traditionally in a chillum or conical pipe. Charas, or hashish, is created by repetitive rubbing of cannabis flower between the palms or over cloth to strip off the sticky resin-bearing hairs (known technically as "trichomes"). This yields yellow-green-brown, crumbly or puttylike hashish. Typically charas contains around 6% THC, compared to perhaps 1%–2% in bhang. Watching the charas preparation process always evokes for me the hand-rolling of fine Cuban cigars.

The custom of bhang consumption during Holi is strongest in North India, appropriately enough in Varanasi, Shiva's devotional city. Bhang preparation on the ghats is common during Holi festival time celebrating the end of winter and beginning of spring in late February or March. Appropriate, wise consumption of cannabis is believed by devotees to enable unity with Shiva, the shedding of sins, and avoidance of future hell by entry into his sacred circle. The last two points are particularly ironic in contrast with the view of marijuana use in some Western cultures. Casual Holi revelers use the substance as a way to get buzzed and to enhance their overall enjoyment of the sights, sounds, celebration, and bonding with friends and family that are an essential part of the festival. Cannabis use in India as a sedative and mind-altering substance dates back to at least the 1st

century BC.

Three expectant Holi revelers sit on a bus carrying them across the Ganges from their small village to the big city of Varanasi. They are generally feeling lighthearted and looking forward to the festivities, except for Arjun, who is a tad glum and preoccupied. The others poke gentle fun at him because he is a little superstitious and can be a worrywart. He is well liked because he is Mr. Responsible, sensible, and pretty much guaranteed to keep an eye on details. If someone forgets to fill their water bottle or bring a warm jacket, Arjun, tall and curly haired, is the first to notice and gently remind them. Vikram, the oldest and shortest, is eagerly anticipating Holi this year. As a youngster he was fascinated by itinerant holy men who wandered through his town and the many legends of Hindu deities his grandmother would share with him. He was entranced by tales of the powerful Shiva. Vikram sometimes imagines what it would be like to dedicate your whole existence to seeking transcendence as a wandering sadhu, and how different that life would be from the professional career path he has embarked on. The third musketeer, Devendra, with his faint, wispy moustache, is the joker in the pack. Lighthearted, always enjoying the moment and outright silly at times, Dev is always ready with a quip. Family members and teachers accuse him of not taking life seriously enough, but he feels, at 16, that there is plenty of time for all that in his future, just not now. Right now life is about having a good time and hanging out with his friends.

Just before dawn, ushered in by the embers of the previous night's bonfires and torches, Holi begins with a faint remnant of the smell of burnt wood. The little band stops at a stall to sip some sweet chai, so painfully saccharine that Devendra jokes that the dentist back home must be in cahoots with the skinny stall owner. The group rapidly runs into a mad crush of hustling and bustling people. Chatty tourists with long-lensed cameras, stall owners touting their wares, brightly beturbaned locals, orange- and saffron-robed religious figures with colorful patterns drawn on their foreheads, white-bearded religious figures, beggars looking imploringly from mats on the sidewalk, Vedic astrologers, and razor-wielding barbers looking for customers have already made it to the riverside and are congregating around the ghats. It's not just the mass of humanity, the individual bodies with a common purpose, but in the half-light by the pea-green, syrup-slow Ganges flowing from the south, there is abundant evidence of animal life. Roosters crow, chickens cluck, pigeons flap, dogs bark and snuffle on the shore. Mooing, placid, long-eared, sad-eyed cows wander about, and the occasional screeching monkey solicits scraps. Adding to the symphony, someone is chanting a prayer in a raspy, slightly off-key voice that Dev claims was stolen from a frog. Vikram and Arjun chide Mr. D. for being disrespectful.

Along the streets, wood fires flare irregularly and help guide the travelers. Some flames are heating cauldrons of delicious-smelling food. This is a religious city, and the fires remind the three friends that a few streets over, in the two special riverside burning ghats, corpses are being cremated. Here in the holy city,

their former owners are thereby freed from the eternal cycle of death and rebirth. The elderly and ill are drawn to Varanasi to live out their remaining days before being released from earthly suffering in clouds of smoke. The river itself cleans and purifies the living through immersion, and a little later in the day, pilgrims will be dunking themselves in the healing waters. Legend has it that at the beginning of time, Shiva let the Ganges burst forth from a lock of his hair in a cataract of clear, holy water.

Arjun, Vikram, and Dev reach the broad river shoreline exactly as the sun rises on the opposite bank. Vikram claims he can see their hometown way over there, amid general skepticism from the others. Hundreds of tourist camera shutters click and chatter at the same time as the huge red orb is reflected in the river. The sun begins to pick out clumps of people boarding bright-colored boats on the shoreline, and women beating clothes on planks and rocks to clean garments in the river as discarded floral garlands float by. Having served their purpose, the lamps that exist to help guide nocturnal spirits home, craning their necks over the river on long wooden poles, are extinguished. All over the city, endless rituals continue in a thousand temples.

The three friends wander away from the ghats and climb the slight hill back to the throngs of people who are already enthusiastically eating and drinking, sampling pastries, sweetmeats, and occasionally alcohol, chattering away amid the colors of joy and excitement. In the thoroughfares, containers of flowers and garlands are displayed on plates. Street merchants stand by enormous sacks of colored pulverized cornmeal, whose rolled-back tops reveal interiors already intensely dyed by the contents. The brightly hued powders have already been partially spooned into plastic bowls ready for weighing and bagging. As bicyclists leisurely pass by and pedestrians jostle, the stall holders arrange the bowls, scales, weights, cups, and ladles to make their wares more attractive and competitive. Nearby, on the stone blocks in front of a temple, flanked by chairs, red cloth flags on the tips of long poles wave over the jostling throngs of men, women, and children. Above the crowd, the wind flaps and snaps the banners, stirring a complex smell of sweat, tobacco and ganja smoke, cooking food, burning charcoal, goat blood, and animal dung.

As the boys make their way down the street, they are met by chromatic explosions of brilliantly colored powders of the most vivid hues, flung high by revelers, resembling a cottage garden on acid. Vivid purples, yellows, blues, greens, scarlets, and oranges are sometimes singular expressions of colored joy. At other times, the eruptions are mysteriously coordinated, emerging vertically from a thousand places in the huge crowd simultaneously, swirling together in the air. There is a Day-Glo ocean of particles and rainbows of psychedelic dust, as devotees fling handfuls of colored cornstarch heavenward. Others toss tinted water-filled balloons or spray dyed water at each other. All these colors mix and spiral in the resulting puddles beneath everyone’s feet that reflect the temples, the sky, and the crowd. Dull brown sparrows splashing in the bright-hued liquid look as striking as parrots for a few gorgeous moments, before they shake themselves

off and fly away.

The bedazzled crew wanders over to a large stall where bhang-infused drinks are being concocted from scratch. Like amateur foodies watching cooking shows on TV, they find the process inherently entertaining. To prepare the bhang, boiled female cannabis-plant leaves, buds, and stems are being ground by a young member of the stall owner's family into a dark olive-green paste. This traditional grinding process uses simple slabs of worn stone. The higher-end stalls with fancy prices two streets up use expensively crafted mortars and pestles, but the end result is identical. The resulting smooth cannabis paste is mixed with a slurry of nuts and spices. Slapped together by hand, the mixture is mounded into baby volcano shapes or rolled into tennis-ball sized spheres and rubbed and filtered methodically through a fine cloth net into steel buckets. Because THC is so fat-soluble, cannabis-laced drinks are prepared with ghee (clarified butter) or milk in some form to aid its absorption. The resulting gallons of milky, slightly murky, green, and mildly psychoactive fluid await.

The stall owner asks if they're actually going to buy anything or just gawk, so each of them purchases a generous cup full of cool, fragrant, and refreshing bhang thandai. This drink is created from boiled milk plus a delicious-smelling ground-up potpourri of crushed rose petals, sugar, cardamom, dry nuts, peppercorns, fennel, poppy and melon seeds, and aniseed. And of course the main attraction—bhang. The concoction is ladled from a large jug into bright copper cups. Saffron strands float invitingly on top. Vikram and Devendra order "medium strong," and Arjun pays a tad extra for "strong." Traditionally thandai and lassi are drunk with the head back, mouth wide open, and poured down one's throat without lips touching the vessel. All three of them somehow manage this procedure without spilling a drop.

A little knot of mildly confused but friendly Australian tourists in their early 20s, attired in brand-new safari clothes, wanders over to ask for an explanation of all things bhang. Arjun enters professorial mode and explains that there are two main bhang-based beverages consumed during Holi. Thandai is made from boiled milk and is exotically flavored. "Like everything in your mom's spice cabinet mixed together," jokes Devendra. Bhang lassi is similar, but the base is yogurt not milk, so the taste is pleasantly sour. Then there are the many variations of green-colored foods. Halvah is a nutty, sugary sesame confection, blended with bhang for the holiday. Bholas are chewy grape-leaf-colored ping-pong-ball-sized spheres of bhang and other mysterious ingredients. Finally, if you're itching to get high but are not hungry or thirsty, you can always smoke ganja leaves or charas, which is hash, Arjun explains. Unlike bhang, ganja and charas are technically illegal, but during the festival this ban doesn't seem to be very strictly enforced. The tourists introduce themselves, ask many questions, take many selfies, purchase bhang lassi at the stall, and hang out with the Three Musketeers.

Everyone mellows out as the morning unfolds and Holi swirls around them. The frantic rush seems to settle down a tad. Everyone's feeling gently chill, soothed, easygoing, and slightly silly. Devendra is the predictable catalyst for the

latter. He launches into recounting a recent online news item about wild parrots 500 miles west in Madhya Pradesh who are addicted to opium. Flocks of these brightly colored birds dive into the poppy fields to nibble on the ripe pods, or even snip them off to fly away with their illicit booty. Devendra has the group in hysterics with a passable imitation of a stoned and wobbly parrot, with his wings/arms outstretched, colliding with an imaginary tree. One of the Australians launches into a riff about wanting to be reincarnated as a bird, which somehow elides into birdseed back home being made of hemp and the phrase "stone the crows." Devendra claims that Arjun has already been reincarnated as a vulture, because he's always hungry. Arjun agrees, and to illustrate the point, wanders off in search of a snack. He brings back a small plateful of bhang-stuffed bholas to share with the group. One of the tourists takes a bite and, after chewing the confection, describes it as "weird stoner marzipan." Devendra makes the outlandish claim that the main bhola ingredient is frogs. For one reason or another no one else seems tempted, so Arjun, channeling his inner vulture, polishes off the remainder. One of the tourists has a kazoo, which sparks group hilarity about loud, cheap plastic and terminally annoying vuvuzelas and their kinship with the clay chillums in which the holy men smoke ganja. This is followed by much speculation about the effects of smoking marijuana through varied musical instruments from saxophones to gigantic William Tell–style alpenhorns.

Somewhere in the proceedings, the plateful of unwisely eaten bholas kicks in for Arjun, who notices that his heart has speeded up and is pounding unpleasantly like a tabla drum in his chest. An uncle had died of a heart attack a few months back, and Arjun dwells on this memory, feeling simultaneously sad and anxious. He hopes his own heart is okay. Maybe it's not. Events are becoming steadily less comfortable, and his achy chest is worrisome. Arjun excuses himself and quickly wanders away from his old and new friends to chill out and get a little alone time.

As he makes his way down the street, the whole festival begins to feel oppressive. The colors are a little too bright. People seem to be looking at him and giggling. His thoughts swirl. Everything is off-kilter, as if the world has changed in some unpleasant and scary way. He clearly recalls he had this same feeling the last time he used cannabis. This time around though, the state is much stronger and harder to rein in. There has been a lot of talk in the press recently about a new satellite launch in India. Suddenly Arjun begins to worry that maybe the satellite is somehow tuning in to his thoughts and broadcasting them to people in other places around the world. Part of him knows that thought makes no sense. He suddenly becomes aware of fearful looks on the faces of young women in the throng, who seem wary of the glances they're getting from the group of men on a street corner. He's worried that he might be responsible for this in some way. His thoughts are bouncing around a little fast and randomly, so it's hard to keep track of them. The pervasive tone is edgy and unpleasant, with little rivulets of upset turning into a powerful waterfall of negativity. Arjun has the strange feeling that he can see his own soul and the souls of those all around him. Each soul is a small, fragile white worm, like the wriggly grubs he had seen as a kid in a sack of old lentils. This idea

feels very strong and important but makes him feel small, insignificant, and vulnerable. He could easily be squashed. His swirling thoughts return to his dead uncle. When he looks into a nearby puddle, Arjun does not see his own reflection, and it occurs to him that he might have died. This leads his mind to Vaitarani, the river full of human bones, sharp fingernails, and filth where sinners are tormented. Everything's spinning a little out of control. But the rational part of his brain kicks in, and he makes his way to the emergency medical tent at the end of the street. Everyone there is helpful and reassuring. They talk to him calmly, asking him what's going on, measure his pulse and blood pressure, and tell him that he's feeling the effects of a few to many sweetmeats. And next time don't order the strong thandai, they caution. They give him a cup of hot tea and make him feel relaxed. Slowly, and it's hard for him to say exactly how long it takes, Arjun notices that everything is coming back to normal, his thinking is clearer, and the anxiety is fading. After a brief check with the staff, he wanders back a little shakily to find his friends.

Meanwhile, shortly after Arjun wandered off so abruptly, Vikram waves goodbye to the group too. He is in search of one of the many groups of Shiva devotees. The Hindu community provides free marijuana for these holy men, or sadhus, who neither work nor have family ties. They are supported entirely by donations from the community. The sadhus cover themselves with a simple loincloth and paint their bodies with sandalwood ash or dye. They tame their physical bodies and earthly desires through yoga practice. Some assume painful postures, sometimes for extended periods, even years, tolerating suffering. Thus by their prayer, austere bare-bones lifestyles, fasting, and bodily deprivation, they atone for their own sins and those of the entire community. Part of Vikram feels respect and admiration for the sadhus, in part because he knows that he could never pursue such a life himself. He respects the fact that as a type of human scapegoat, they achieve self-liberation through worship, yoga, meditation, and reflection on the divine and of Shiva in particular. As a key part of this mode of life, smoking ganja frees the mind to aid calm contemplation of the infinite. And Shiva himself legendarily consumed marijuana as a blessing.

According to the Indian Hemp Drugs Commission Report of 1894 (which we will discuss later),

> these religious ascetics, who are regarded with great veneration by the people at large, believe that the hemp plant is a special attribute of the god Siva, and this belief is largely shared by the people. Hence the origin of the many fond epithets ascribing to ganja the significance of a divine property, and the common practice of invoking the deity in terms of adoration before placing the chillum or pipe of ganja to the lips. There is evidence to show that on almost all occasions of the worship of this god, the hemp drugs in some form or other are used by certain classes of the people.[2]

Vikram perambulates along a narrow brick-lined street toward an area with many temples. He passes a striking-looking pink-robed, be-necklaced man with a pink turban, shoulder-length black hair, and a long windswept-looking white beard. Vikram continues his thought that after smoking ganja, everyday feelings and concerns disappear for the holy men, who become one with the universe. The space left by the loss of their individual self-identity and earthly cravings fills with

religious insights about Shiva, and concentrating on God is more easily attainable. Lost in his contemplation, he is given a wide berth by bareheaded women in red and purple silk scarves. He presses on and, guided by the sound of religious music, finds his way to a large room in a shabby temple complex.

Vikram wanders tentatively onto the threshold to be greeted by the sight of an elderly bearded man seated at a large wooden table. He is chopping light brown ganja leaves on a copy of the local newspaper. The old fellow is using a double-edged metal knife very proficiently. The sunrays from a window way up on the wall shine on him directly as he slices methodically at the dry material. One of his companions helps mix the leaves with shredded cigarette tobacco and layers the contents into an 8-inch-long clay chillum, or vertical cone-shaped clay smoking pipe. Vikram thinks back to the vuvuzela jokes, and he smiles. A man who could be anywhere between 30 and 70, with dreadlocked hair braided into a loose bird's-nest topknot, beckons him in. The man's forehead is painted with wide stripes and dots of yellow and white paint contrasting with his brown skin. Another celebrant has lit the chillum, wrapped its narrow lower part in a rag, and is taking giant leafy puffs. Eventually an arm with a well-worn pink string wound around a hairy wrist passes it to Vikram. After inhaling deeply, he too passes it on to the person next to him. This man has dilated pupils in deep-set eyes under a set of bushy black eyebrows and a long, seemingly never-combed beard. He acknowledges the gift of the pipe, and soon he too is huffing and puffing.

On the other side of the room, a group of traveling musicians is performing devotional songs. Some strike rows of coin-sized silver cymbals on metal bars. Others perform on saucer-sized brass cymbals, tabla drums, or sitars. Seated on the floor, several singers accompany the instruments. Light streaming through windows highlights the details of their robes, colored turbans, and painted faces. Some of the musicians smoke ganja to concentrate on Shiva, who is thus honored, as they sway and clap to the rhythm. With the ganja, their timescape slows, and they can focus keenly on both the individual parts and overall patterns of the changing music.

Vikram is absorbed inexorably into everything going on in that room. A man with thousand-year-old eyes and a golden-yellow spot between his eyebrows smiles beneficently at him. He is attired in a reddish cloth wrapped around his waist. Vikram notices the man's long fingernails and dirt-covered bare stomach. One holy man lights the chillum for his neighbor. Friendly brown faces around the room bear various wrinkles, paint, noses ranging from long and aquiline to snub, and expressions ranging from rapt to blissful. One sadhu looks to be aged about 70 with bags under his rheumy eyes. He has a thermometer-shaped red streak running the entire length of his forehead then plunging beneath his headscarf. Vikram becomes aware that the chillum has a white turban of ash sitting on top of it. A younger sadhu dressed in a white silk shirt puffs furiously before inhaling. The rag around the chillum's lower part is now nicotine-stained but doing its job of preventing burned fingers and lips. Meanwhile a smooth pebble at the bottom of the chillum stops the user from injudiciously sucking burning coals of weed into

his gullet. Vikram's mind drifts slowly to some other place, where he feels the benevolent gaze of Shiva penetrating and illuminating everything. Vikram is both detached yet completely part of everything going on around him. He knows that the earth is made of music and that its rhythms paint and disclose our world and, in turn, reflect the rhythm of the universe. High above in the heavens, the great iron wheel of cause and effect turns slowly and portentously. Its hub is in the center of the room with them all, thrumming and vibrating. Vikram sees himself seeing and feels the inevitability and liberation of death and rebirth under the eternal Eye of Shiva.

Back in the street near the bhang lassi stall, Devendra is still relaxing with his new friends. He has slipped comfortably into his usual role as court jester and can intuit what will get the now-inebriated little group giggling and snorting with laughter. They sign on enthusiastically to his suggestion to open a stall selling T-shirts emblazoned with the slogan "I drank bhang lassi in Varanasi." His body feels comfortable, and he's utterly at ease with his companions. He's happy to be out here as part of the milling crowds celebrating Holi. Devendra observes that the festive colors have a depth and brightness that seem unusually magnified. He can almost reach out and touch them with his eyes. He is able to distinguish subtle differences among the various shades and seems to perceive at least 10 hues of green. Sounds and colors and tastes blend together and change places. When he takes a final sip of the bhang lassi, the flavors echo the color bursts and surges. Time is slowing down, and the thrown colors appear blissfully suspended in midair for what seems like an entire minute. Inspired by these dancing hues, Devendra stands up and begins to pirouette comically, but the combination of being slightly uncoordinated and not noticing a slippery patch on the cobbles results in an unexpected pratfall onto his butt, straight into a roadside pool full of brightly colored Holi-tinted water. Everybody in the group, including Devendra, finds this hilarious. As he sits down comfortably, if a little damp, a street-side dandelion catches his attention. The golden-yellow wildflower, relatives of which he has seen a thousand times previously, is unfamiliarly absorbing and utterly beautiful. How could he have never noticed the subtle toothiness of the petals or the delicate, almost-pulsating aura that perfuses the bloom? He's engrossed by this enchanting speck of creation for what seems hours, interrupted only when a woozy Arjun wanders back from the medical tent.

By now, you're either googling "do-it-yourself bhang lassi recipes" or shaking your head in horror, wondering what kind of parents would allow their teenage sons to go to a pot-and-powder party. No matter which you're doing, let's pause and ask what we can learn from this description of Holi. I like to think that one aspect of the festival is to provide a gateway of sorts to marijuana-related issues. After all, this is a venue where cannabis has been used for 3,000 years, for the most part safely. Over this long period, Indian society has worked out how to minimize problems associated with the drug. And in the past 120 years, historical commissions and reports have attempted to understand and document these issues.

Although there persists a wide variety of opinions regarding cannabis and the people who use it, nearly everyone tolerates the festival and, alongside that, celebrations of which marijuana consumption is an inherent part. In turn, public policymakers in the West can learn from, and usefully take into consideration, the experiences and policy decisions of a culture that has done a creditable long-term job of accommodating recreational and religious cannabis use. In other words, Holi provides anecdotes and examples that are important subject matter for scientific inquiry. Thus, it serves as a gateway into the remainder of this book.

Here are some of the major issues raised by our snapshot of Holi. The celebration is a cannabis-themed festival that has been celebrated for thousands of years. But how long have humans used cannabis, and for what reasons? This volume will conduct a very brief historical tour through different civilizations that have used the hemp plant, with its THC-containing sibling cannabis, to provide food, fiber, medicine, religious insight, and recreation at different times and places. We will explore where the plant first grew, and when humans encountered it and helped spread its seeds around the globe.

One key question is how the drug produces its psychoactive and medicinal effects. We investigate the complexities of the brain and body's endocannabinoid system in Chapter 4. Why did all three of the boys we followed at Holi undergo such different experiences? An important observation is that, among individuals using intoxicant-containing chemical varieties of the plant for recreational or religious purposes, different people have markedly varied subjective encounters with cannabis. The rather disparate individual bhang-provoked experiences of our three, albeit unavoidably somewhat stereotypical, protagonists mirror typical reactions of many cannabis users. Devendra got stoned and enjoyed a good time with his new friends. This experience probably outweighs all other outcomes in frequency by a considerable margin. Arjun's anxious, dysphoric, and mildly paranoid reaction to the drug is the rarest. Besides, most individuals who have unpleasant experiences when using cannabis will not willingly choose to use the substance again. Vikram's religious awakening is also relatively less common, although it may be the closest to the original use of religious ceremonial drugs such as cannabis. Chapters 5 and 7 will explore common short- and long-term experiences—both pleasant and unpleasant—of those using the drug.

Our story also illustrates that there are many different means by which one can consume cannabis. Edibles, consumed in India for millennia, were subsequently adopted in the Islamic world and later France in the 1890s but are relatively new to the United States. I interviewed two Indian psychiatrists regarding their experiences after drinking bhang lassi and using cannabis edibles as revelers at Holi. Both agreed that, compared to smoking marijuana in the United States, the effect of the drinks or sweetmeats was distinguished by more of a feeling of mellow happiness and calm relaxation, with more of a body high and less "buzz." One colleague attributed this to the festival setting, while the other speculated that the higher CBD-to-THC ratio of cannabis used typically to prepare these edibles was responsible. Another relevant factor is the total dose consumed; bhang's THC

content is scanty.

Every recreational drug has its yin and yang, risks and benefits, good and dark sides. I try to examine both aspects of the drug as open-mindedly as possible. Chapter 9 probes how recent research illuminates what we know (and mostly don't know) of cannabis's emerging medicinal properties. The 1894 Indian Hemp Drugs Commission Report[2] was the first to enumerate many of these risks and benefits, and one recent controversial book focused more specifically on particular cannabis-associated risks.[3] But what is the magnitude of overall risks associated with cannabis, and how do these stack up when compared directly to those of, say, alcohol or nicotine? Chapter 7 will address these issues.

Earlier we learned that Arjun partook of significantly more drug than the others, which likely contributed (along with his pre-existing worry-prone mental set) to his brief but unpleasant, out-of-control cannabis experience. Chapter 5 discusses which effects of cannabis are most likely to occur in particular dose ranges and why. Deepak Cyril D'Souza, a psychiatry professor at Yale University medical school, is both a clinician and researcher with considerable depth of knowledge in the areas of both psychotic illnesses and cannabis.[4] His research in India examined psychiatric hospital records and revealed a significant upswing in first-episode psychosis admissions to the huge regional mental hospital at Ranchi that occurred in the month following Holi, compared to the month prior to the festival. This observation illustrates what we know from other sources: that part of the dark side of cannabis is its property of raising the risk for psychotic experiences of various kinds. These range from the frightening but relatively harmless to the enduring and destructive. We will parse these various distinct states in Chapter 7 and explore their underlying mechanisms. That portion of the book, alongside Chapter 6, probes how common such experiences are. The book also examines the chicken-and-egg question of whether cannabis use provokes psychosis or vice versa, as well as issues related to cannabis addiction, and the drug's short- and possible long-term effects on cognition and IQ.

The dangers of driving under the influence of alcohol are well known. But how about those of cannabis? Driving on Indian roads can be hazardous under normal circumstances, but the Delhi-based NGO Community Against Drunken Driving (CADD) says that more people die in road accidents on Holi day than on New Year's. Many people believe the accident rate rises because revelers consume both bhang and alcohol.[5] But how dangerous are cannabis-intoxicated drivers compared to drunk ones? And what happens to driving ability when cannabis and alcohol are taken together? Chapter 7 tries to answer these questions. Finally, Berenson's recent book[3] makes explicit (if debatable) links between cannabis and crime. Again, Holi encompasses this issue. Female students complain of harassment by intoxicated men during Holi. When the women protest, the standard response from those pestering them is "Don't feel bad, it's Holi." [6] Whether the links between cannabis and crime are an inherent consequence of using the drug or more attributable social and criminal policies related to cannabis (and their differential enforcement when it comes to ethnic minority groups and people of color) is a

further issue that I will deal with.

Finally, we should note that ganja, charas, and bhang used to be available without constraints in India, until they were banned under the country's Narcotic Drugs and Psychotropic Substances Act in 1985, under diplomatic pressure from Western countries, especially the US. As a result, ganja and charas were declared illegal for both medical and recreational purposes. But cunningly, bhang was exempted from the definition of "cannabis" and as a result can still be purchased in some Indian states from government shops, perfectly legally. Recently, there have been increasing calls for full-on cannabis legalization as India undergoes an agrarian crisis.[7] After all, this is the country for which *Cannabis indica* is named, where the drug has been consumed for millennia and literally grows like a weed across the subcontinent. Thus, Holi lets us revisit the question of national cannabis legalization and encourages the careful review of the scientific evidence for and against this major decision that needs to be addressed in both India and the United States. Lawmakers need to contend with these issues if they hope to stay ahead of the cannabis curve.

Chapter 3

ETHNOBOTANY, BOTANY, AND ARCHAEOLOGY

> I am very glad to hear that the Gardener has saved so much of the St. foin seed, and that of the India Hemp. . . . Let the ground be well prepared, and the Seed be sown in April. The hemp may be sown any where.
>
> GEORGE WASHINGTON TO WILLIAM PEARCE, February 24, 1794[1]

The cannabis plant is a busy chemical factory. What are the different compounds it manufactures? Are all of them psychoactive? Why do these substances exist in the plant to begin with? Do they occur in other plants? When did humans first encounter cannabis and how did they use it—as food or fiber source or intoxicant? Is cannabis a "camp follower" that has traveled with humans across the globe? How has digging up ancient tombs and caves, analyzing pollen, and using modern genetics helped answer these questions?

My visit to the cannabis growery

It's a hot, sticky afternoon in Denver as I pull into the parking lot. Nearing my destination's unassuming but tightly secured front door, fugitive tendrils of a characteristic musky green odor betray what lies beyond. I press the door buzzer. A tall middle-aged linebacker in acid-washed jeans beckons me in, checks my ID, and has me sign for my visitor's badge. This is Andy Williams, director of Medicine Man, often described as the "OG of the legal Colorado marijuana business" and the brains behind this 1,300-square-foot MedPharm facility operation. Chatting with him before we tour the place, he seems slightly awed by the functional beauty of his own sleek, well-staffed new building. As we enter the complex, immediately confronting the visitor is something I mistook for an instant as an animal exhibit at a high-end zoo. Behind a wall-sized tinted inset glass frame looms a room full of lush semitropical greenery. I half expect to glimpse a bug-eyed lemur or sinuous python gazing back at me through the glass, but this room is devoid of any creatures. Here live the cannabis mother plants from which clones are harvested on a regular basis. Their ancestors hailed from Northern California and Amsterdam. And their offspring, the genetically identical clone cuttings, are the most reliable and predictable source of healthy all-female delta-9 tetrahydrocannabinol (THC)-rich flowering shrubs.

A well-known cartoon from the British caricaturist James Gillray portrays the Duke of Bedford looming tall in a stockyard. The digits of his dominant hand proudly grasp the flank of one of the gigantic oxen that he had helped breed. Alongside the physical resemblance, there is something about Andy's gratified stance in front of his mother plants, juxtaposed with a parallel example of the triumph of selective breeding, which immediately echoes the confident duke in this early 1800s print. In this case, the stock is selected for beefed up THC content rather than bulky meat on the hoof. Contrary to my initial assumption, the mother plants are not an immortal clone source. Instead, they are ultimately removed to some horticultural slaughterhouse, yielding their place to a brand-new healthy maternal generation.

Cannabis groweries evoke a palpable tension between the new and the old, perhaps because they exemplify the balancing act between nature and our ever-advancing technology. I appreciate the gleaming silver-and-glass, high-tech, HEPA-filtered, UV-treated, root-hormone-fueled, carbon-dioxide-charged modern ambience. This vibe is somehow familiar. I first encountered this business-meets-science dynamic at a high-school visit to a British chemical factory, yet Andy's environment is different. Where I'm standing, a modern academic science lab has been grafted directly onto Hogwarts. On one hand, every activity is on a precise calendar-driven schedule. The whole facility is meticulously planned out, ranging from the exterior felon-deterrent security bollards to the no-sweat wall paint that discourages potentially plant-threatening molds. The character of the staff is of a piece with the building design. There are plenty of white coats and labwear. Attitudes are polite and businesslike yet enthusiastic. There is nary a stoner reference or pot joke. On the other hand, I also note the semi-medieval alchemical recipes comprising rosemary- and coriander-scented bug repellents, sprinkles of insect-poop fertilizer, and other traditional hand-me-down hippie strategies for driving out thrips and powdery mildew.

Over 60% of MedPharm's floor space is dedicated to growing cannabis plants. The healthy little 4-inch clonal babies are snipped carefully from their mother plants under the watchful eye of the security-camera domes that peer constantly at every interior and exterior surface. Their infant stems are dipped in powders to help them grow strong roots, and then they are whisked away to a room to be potted (by definition), sorted into black trays, and eventually arranged by strain. Medical plants go to one destination, recreational ones to another. This sorting is necessary because different state rules and regulations apply, depending on the product's ultimate purpose. Soon after these plants begin to show growth, their peaty roots are embedded in cream-colored grow cubes the size and heft of a building brick. By the end of 9 or 10 weeks, many of these grow-bricks are decorated superficially with green marble swirls of algae that can be handily sliced off at the next stage. This involves the cubes being embedded in what look like bucket-sized plastic wraps full of artificial soil. I spot hundreds of these beefy healthy-looking 2-foot-high plants in individual white baggies within their new home at one end of greenhouse number one. Every horticultural activity

throughout the cannabis growery is tightly time-driven to fit precisely five and a half complete growth cycles into a calendar year. Irrespective of the outside temperature, which today is sweltering, in this segment of the operation, it's always 78°F. And in the brave new world of the cannabis greenhouse, every single plant is a pampered alpha.

By the time the plants are ready to move to greenhouse number two, they look much more mature. They have been "schwazzed," Andy tells me. In this process, many of the fan-shaped leaves are stripped off, in a procedure also known more formally as trimming or pruning. Schwazzing forces the plant to concentrate on building a strong "core" of strong roots and robust stems. Later, the process is repeated, this time to push the plants to concentrate on growing luscious buds and flowers, rather than large, THC-poor fan leaves. In the controlled environment of this mega-grow greenhouse, there are top-to-bottom and cross-ceiling pipes of all shapes, colors, and sizes. White-insulated, bare metal, or mixtures of polished metal and black cladding, they are ubiquitous. One way or another, the processes they embody maintain the desired atmosphere and temperature. I'm shocked by the relative coolness of 78°F. I was expecting a tropical orchid-house-like muggy heat somewhere in the 90s, but of course that would kill the cannabis plants. Everything here is controlled by the pipes and wires, including the light, temperature, humidity, and carbon-dioxide concentration. The lights (some blue, some red at this stage) are turned on for 18 hours a day to bamboozle the plants into thinking that it's springtime and that they need to grow quickly. Later, the light wavelengths are tweaked to be progressively redder (it's fall, guys!) to encourage flowering. The cannabis thrives in the high humidity, but so too do mildews. A classic garden battle is waged constantly against the potentially devastating powdery mildew under the relentless glare of the specialized lights. As well, various rots, bugs, and other critters can attack the plants and must be guarded against in this never-ending war.

Andrew, the head gardener, moves busily in an adjoining room, supervising huge polyethylene vats containing hundreds of gallons of water and blends of murky brown nutrients. These are the extracts that are mixed prior to watering the burgeoning plants one by one with special spray wands. Andrew is a polite, intense individual in his late 20s, full of arcane and fascinating information regarding cannabis cultivation. Keeping a careful eye on the processes behind him, backlit by the somewhat glaring and surreal grow lights, he peppers his conversation with specialized gardening terms. I scribble down "canopy depth," "pythium root rot," "spider mites," "powdery mildew," "fusarium wilt," and "hops latent viroid" to check out later. As we all gaze appreciatively over the serried ranks of clones, I realize that Andrew is not simply tuned in to the overall esthetic but is a proud father doting on his clonal babies. There's a reason they call this place a "nursery." In addition, I sense in him the slightly wary attitude of a watchful epidemiologist, his ever-observant CDC-like antennae twitching for a potential patient zero to appear in his greenhouse. Such an intruder will require a quick squirt of this or that treatment to halt the epidemic.

Moving next door, a young woman wearing a black baseball cap, black medical gloves, and navy medical scrubs is supervising the drying room. This space is where Christmas-tree-sized plants hang upside down on racks like aging beef, curing to 3% humidity under gentle heat. When they are ready, the drying supervisor will remove the buds and leaves in the adjacent strip room. From there, they are transported to a nearby space for bagging the former and grinding the latter. The buds are sorted on heavy institutional battleship-gray plastic carts topped with trays. From each cart, the dry buds are shuttled efficiently into translucent greenish plastic sacks, roughly the size of the leaf bags seen on northern lawns in the fall. I want to ask whether the bagger is tempted to take the occasional sample home, but the ever-present domed security cameras answer my question. The leaf grinder is not a person but a sleek steel funneled piece of machinery on shiny metal legs that would not look out of place in a very high-end coffee roastery. From its belly protrudes a flexible tube that conveys the precisely chopped lower-THC plant parts to the neighboring extraction room, the habitat of Devon. A slightly built wispy-bearded man in his 30s, Devon runs the arcane six-hour carbon-dioxide-driven extraction process. This necessitates pressurized gas being forced through gleaming steel, blue-topped canisters, each of which holds around 15 pounds of plant material—the shredded stems and lower leaves. The carbon dioxide assumes some super-critical meta-state between gas and liquid, driven by a huge lime-green-painted pump, quietly chugging and puffing away in one corner of the extraction room. This is the single device in the entire operation that is distinctly non-21st-century. It would not be out of place in a 19th-century fun fair, powering a merry-go-round or calliope. The cannabinoid-rich extract removed by the CO_2 is filtered, and part of it is “winterized” by refrigeration. The rest of the resulting brew is then swished with alcohol and transferred behind the large safety-glass panel of an expensive-looking 5-foot-tall laboratory-white machine. On the other side of the glass, a mysterious slowly rotating foot-wide orb is ensconced in a steel vat of precisely temperature-controlled water. Its purpose is to gently boil away the alcohol under a vacuum, separating it from the remaining molasses-colored plant distillate. The orb’s surface mirrors a tiny spinning reflection of the room’s inhabitants and the overhead fluorescent lights.

Once all the alcohol wafts away, the remaining valuable chemicals are separated into their key constituents. The finished process yields a variety of compounds that are decanted off. I’m shown an example of one such product. It resembles a large honey-filled mason jar. When this glass container is tipped upside down, however, the contents with their luxurious, glassy, almost amber-like consistency are reluctant to trickle down the side of the vessel, barely moving. This 700 g of almost pure THC can’t decide if it’s solid or liquid; clearly it already has its own built-in couch lock. Another pure distillate derived from the distilling process is a small vial of fresh green, almost fluorescent, liquid terpenes. Sniffing it, I expected to be overwhelmed by a big harsh green smell akin to an entire pine tree and a couple of skunks in a vial. Instead, I’m surprised by the pleasant subtle, low-key, vaguely lemony verbena scent, with the barest hint of evergreens. The

terpenes can be blended back into the purified cannabis compounds such as THC for both flavor and "entourage effects," above and beyond those of the familiar cannabinoids. Some people term this green material "terp sauce." Yet another jar in the chemical goodie cupboard looks to me as if it's full of solid cream-colored coconut oil; these plant waxes are yet another byproduct of the extraction process.

Next, our group enters the test and formulation labs, where young brown-eyed, white-coated Stephanie shows us around. In this sterile room, mandatory quality control of the various products is carried out on a high-performance liquid chromatograph and mass spectrometer (LC-MS). Up to 10 different cannabinoids can be assayed here in less than 15 minutes. The different compounds travel at unique speeds through the device, and the height of the resulting peaks generated by the machine correspond to their individual concentrations. Stephanie peers carefully at this mini mountain range of data through her glasses, and we move on to the gas chromatograph–mass spectrometer (GC-MS), whose purpose is to perform additional assays. Around the corner is yet more equipment, dedicated to detecting possible microbial or fungal contamination.

We continue into the formulation room. This boasts the contents of a manufacturing pharmacy. There's an ointment mill, a tincture blender, a machine for making pills, and most interestingly a process for making water-soluble THC powder. This off-white fluffy material resembles the result of somebody whacking the pumice stone in their bathroom into coarse chunks. As Stephanie holds up the jar, her pale pink nail polish provides contrast against the 23% THC material. She explains that a patented encapsulation process birthed this fluffy stuff. This involves mixing pure THC with a secret powder in a volatile solvent and then vaporizing off the solvent to leave behind the chunks of residue. These can be ingested without the need to dissolve them in anything oily or fatty, merely by stirring them into water or juice. Next, I sniff the selection of cannabinoid lotions and creams compounded here, and we learn about various research projects and experiments. Some of these aim to develop injectable compounds, to improve the vape formula, and to formulate new tinctures. I inquire about edibles, and I'm surprised to hear from Andy that MedPharm does not venture into this area. Legislators are wary of them, particularly of the possibility of accidental ingestion by children. Consequently the regulations and labeling requirements for edibles are apparently stringent and ever-changing. Finally, we end up in the packaging room. While I'm appraising the container-loaded pallets, my phone buzzes to remind me that I have a plane to catch, so I thank everybody and head out from cannabis central and back on the road.

What is cannabis? What's the difference between cannabis and hemp, how do we classify them, and why does it matter?

Cannabis is an annual plant belonging to the mulberry family and related to hops, which dies at the end of each growing season. It propagates itself through seeds grown from the female plant after fertilization by pollen from the separate male

specimen. Some cannabis leaves (like those on deciduous trees) turn golden brown in the fall. At this time of year, the flower clusters can be shot through with purples, pinks, reds, and oranges. Bunches of female flowers can fuse together into long, lumpy aggregates that are sometimes called “colas” (from the Spanish word for “tail,” not the soft drink). In their song “Hotel California,” the Eagles sing of these little cannabis foxtails, or “colitas.” Hidden within these female flower clusters are the wannabe seeds, one to a flower. Each potential seed is swaddled by a concentric spiral of small modified leaves packed full of THC. There is far more THC here than in any other part of the plant.

Here’s how events have played out historically. The original indigenous cannabis plant from a particular location has been cultivated by humans to serve a particular purpose. For cannabis there are four separate such reasons: long tough hemp fibers that can be spun into yarn, ropes, or textiles; nutritious seeds that yield oil; and finally, chemicals with both intoxicating and healing properties. Humans generally choose the best specimens of useful plants to propagate—in this case, those with the strongest, longest fibers or most fragrant, intoxicating properties—and improve them over time by breeding. Being the messy species that we are, human-bred strains travel alongside us as we migrate, and they escape back to nature as we drop seeds or neglect to pick them up when harvesting. These mislaid seeds adapt to the local conditions in terms of soil, water, and weather, and some are selected by nature to thrive best in the local environment. Left to its own devices, the natural ability of the cannabis plant to disperse itself over large distances is pretty limited. Author, journalist, and professor Michael Pollan has suggested that cannabis has relied on humans to spread itself successfully far and wide.[2] After several generations, these inadvertently sown plants establish themselves to thrive in the spot where chance deposited them, becoming what botanists term “landraces.” To further complicate things for botanical classifiers, these newcomers may interbreed with their original wild ancestors. That tendency has not deterred modern-day cannapreneurs from trying to hunt down the ancestral native cannabis flower. Back in the 1960s and 1970s hippy pioneer marijuana breeders traveled to central Asia, India, and Afghanistan to look for traces of the original holy-grail cannabis parent plants. They collected the landraces growing there to breed back in the United States, much as current gardeners collect heirloom tomatoes as living representatives of older classic varieties. But whether the hippy-gathered landraces were true ancestor plants or merely feral offspring of long-ago human agriculture is anybody’s guess.

The fact that hops and cannabis are “cousins” botanically speaking is of interest. Hop plants produce the terpene compound humulene, found in some cannabis chemovars that we will encounter in Chapter 8. This (and other terpenes shared with cannabis) may be the reason that hops are said to possess mild psychoactive properties. Some natural-products aficionados sleep with hop-filled pillows, claiming that it cures their insomnia and encourages vivid dreams. Hops are also used to flavor beer (it’s what gives India pale ale—IPA—that characteristic bitter taste). When I lived on an old farm in Maryland, one of my

friends came by to present me with an “interesting proposition.” By his calculation, because of the close family relationship between cannabis and hops, one could grow cannabis and hops seedlings, and when the time was auspicious horticulturally speaking, cut off the cannabis leaves and graft the hop stem and leaves onto the cannabis rootstock. According to him, this procedure would produce a hybrid that ostensibly resembled a regular hop vine but that would covertly synthesize the same quantities of cannabinoids that would have been manufactured by the original cannabis plant. Because it resembled a hop plant above the ground, it would fail to draw attention from law enforcement. Surveying my 2-acre field appreciatively, he said, “And once those hops are ripe, we will have enough weed for ourselves and a couple of hundred buddies. We can both retire in five years.” I told him politely that, while I sincerely valued his friendship, it didn’t extend to going to jail on his behalf.

Where and when in the earth’s history did cannabis first emerge as a distinct plant?

Analysis of ancient pollen sheds light on this question.[3,4] Every known plant produces a one-of-a-kind pollen grain. Under a microscope, these motes can look as different as spiky chestnuts, corals, bath sponges, bats, bowling balls, death stars, doughnuts, and seashells. Worldwide, there are over one-third of a million distinct pollen types. Contrary to my expectation, cannabis pollen is dull colored and small, resembling a tiny olive-green navel orange. Individual grains are far too small to be seen with the naked eye. Half a dozen of them end to end would just cross the width of an average human hair. Each one is the right size to be wafted by a barely perceptible breeze into a cloud of its million-fold companions.[5]

Pollen experts are known as “palynologists.” Pollen grains can be used by forensic palynologists to construct the “travel history” of an item, based on its exposure to the unique regional plant mixture characteristic of various global locales. The US State Department uses pollen to check the origin of imported illicit drug samples. Unique blends of pollen grains have even been proposed to be added to firearm ammunition cartridges for forensic identification purposes. Because pollen grains can endure for thousands of years, archaeologists use them to reconstruct the flora of long-vanished environments and of ancient crops.[6] Prior evidence for the origins of cannabis based on the distribution of wild-type plants suggested that it is indigenous to somewhere in central Asia. Tracking the unique pollen of cannabis back to its origin by combing through ancient soil sediments would seem to be the way to figure out the answer to this question. But hops pollen is confusingly similar to that of its botanical cousin cannabis and easily throws researchers off the trail. Now, using an ecological proxy analysis—that is, deciphering those archaeological and geological sites where cannabis pollen co-occurred with open grassy treeless terrain (different from the locations where hops prefer to flourish)—scientists can distinguish the two. Using this approach, the palynologist John McPartland cleverly separated cannabis’s divergence from the

“joint” family with hops to discover that the two plants split into distinct species nearly 28 million years ago.[4] The evidence takes us all the way back to a region in northeast Tibet near the Steppe community around Qinghai Lake, a region located 10,500 feet above sea level on the Tibetan plateau. From there, pollen tells us that cannabis dispersed east to East China by 1.2 million years ago, west to Europe by 6 thousand years ago, to India 32.6 thousand years ago, and to Japan approximately 12 thousand years ago. This dispersal happened partly by natural spread but presumably mostly by people adopting the plant and traveling, taking the seeds with them on their journey.

The present-day climate in the Qinghai Lake region where ancient cannabis originated is harsh and unforgiving. It has an average altitude of over 4,000 m, low levels of oxygen, low temperatures, strong bone-chilling winds, and intense ultraviolet light. Or, if you prefer to believe the puffery of local tourist brochures, “This idyllic region located not far from the Silk Road is centered around an enchanting, elliptical blue-green lake teeming with easy-to-catch fish and surrounded by mountains, with innumerable varieties of lovely birds flying overhead.” [7] According to an article in China daily *Xinhua*, archaeologists have confirmed human activity around this lake dating back more than many thousands of years.[8] Dozens of stone tools have been found at the same site, showing that prehistoric humans lived, hunted, and made tools in the harsh and chilly environment over 10,000 years ago. So much for the stereotype of stoners relaxing on the couch in the comfort of their own centrally heated basement. Curiously, Qinghai is located only a couple of hundred miles away from the Denisovan cave where 160,000 years ago humans distinct from both modern humans and Neanderthals dwelled during the Ice Age. Cannabis pollen has been found in the layers of soil excavated from that cave.[9] These various observations inevitably give rise to speculation about when humans first paid attention to the plant and began cultivating it deliberately. So, when did that happen?

When did the cannabis plant translate into human agriculture?

Cannabis is one of the world’s oldest cultivated plants.[10] There’s an ongoing debate about which humans where first deliberately grew it, but one group of scholars defends the viewpoint of earliest use in central Asia or China. This cabal fights it out with others stating claims for East Asia and the Steppes. The earliest archaeological evidence for cannabis pollen occurring next to crop pollen, or where cannabis seeds (from a botanical point of view, “fruits” or “achenes”) have been found in archaeological sites, is in Japan. Seeds there from twelve thousand years ago have been excavated attached to shards of pottery. Next, traces of cannabis appear in China. Recent analysis makes a strong claim for even earlier use.[11] According to a recent survey from the German Archaeological Institute in Berlin, by about eleven thousand years ago, evidence of cannabis use appears in Europe and East Asia. Nomadic traders known as the Yamnaya seem to have entered Europe and the Middle East from their homeland in the eastern Steppes in

current Ukraine and Russia around five thousand years ago. They arrived bearing knowledge of metal crafting and herding and participated in a lively trade in cannabis seeds, millet, wheat, barley, and horses across the Steppe zone. The Yamnaya people also left traces of their genes in most of the populations that live currently in Europe and South Asia.[12–14] This dating is inferred from a systematic trans-regional review of evidence from archaeology, and analysis of distribution data from cannabis pollen, seeds, and fibers. The German archaeologists found plant remains and residues in numerous Yamnaya dwelling sites across Ukraine and Russia.

Hemp has been cultivated for its strong, durable fiber and nutty nutritious oily "seeds" (achenes). The desirable long, tough fibrous threads inside hemp stems are harvested traditionally by soaking them in water until the outer stem decomposes, in "retting ponds," leaving the fiber behind. These ponds are remarkably malodorous, and the smell of rotting cannabis stalks is definitely an acquired one. Fiber can also be gathered by crushing the stems. Hemp plants produce cannabidiol (CBD) mainly in their leaves but manufacture no THC and are therefore not intoxicating. In essence, you can smoke hemp till the cows come home and never get stoned. Hemp threads are traditionally woven into mighty ropes, often used aboard ships, spun into strong cloth used in ship sails (the word "canvas" derives from cannabis), or spun into somewhat coarse material that can be worn as clothes. Hemp also makes strong, durable paper, and banknotes can be printed on it. Hemp has been grown in the United States for many years, including by such notables as George Washington and Thomas Jefferson. During World War II there was a short-lived "Hemp for Victory" campaign to produce material for naval ropes.

Nowadays, processed hemp fiber and hemp seed oil are imported from Canada and Europe, as is sterilized hempseed for bird food. Spaced a few feet apart, hemp grows like little bushes; planted in close proximity, the plants crowd each other and compete for light. They attain this by reaching skyward, concentrating on developing long, thin, leggy bamboo-like stems packed with dense, lengthy, tough fibers. Hemp seeds are full of nutritious oil and protein. They were grown as food thousands of years ago, and oil was extracted from them by crushing. Hemp seeds can still be found in health-food stores today; I use them in my morning smoothies. These seeds, sterilized so that they will not produce baby plants when they fall to the ground, are used in inexpensive bird food in the United States. Hempseed oil is also used to manufacture paints and varnishes. Hemp oil rapidly becomes rancid, so when used for food it needs to be consumed quickly after production.

Growing cannabis crops for drug harvesting is a completely different proposition. It relies on different plant varieties that have been bred to contain intoxicating THC. Recall that there are separate male and female plants. Both hemp and drug cannabis are pollinated by windblown pollen, dispensing with the necessity for bees, moths, birds, or bats to do the job. The male flowers resemble miniscule pale green bells. Because the female flowers don't have to signal

gaudily via bright colors or seductive fragrances to attract any pollinating critters, they can afford to be inconspicuous. They are green and tiny, consisting of what botanists refer to as “stigmas.” Delicate, fuzzy, and sticky-tipped, these pollen traps hang together in clusters, poking a mere fraction of an inch out of what look like shambolic clusters of mini leaf tips and untidy flower clusters at the top of the female plant. These latter are the colas we referred to above. If you want to see what these structures look like under a microscope, you can admire their sticky green beauty in Ted Kinsman’s wonderfully photograph-filled book, *Cannabis: Marijuana under the Microscope*.[5] Up close and personal, the stigmas are the palest of pale green, resembling spindly, twisted hummingbird tongues reaching out in all directions to seek pollen. When it comes to THC and its intoxicating band of chemical relatives, the lion’s share of these cannabinoids forms in the female plants, specifically as sticky resin in their flower buds. In the wild, the minimalist male flowers shed pollen that’s puffed by the wind, some of it reaching the eagerly awaiting female flowers.

Since wind pollination is extremely inefficient, male cannabis plants must make far more pollen than ever reaches the females. Having evolved to float efficiently and to stay aloft in wind currents, these billions of pollen grains waft on the breezes until gravity or rain ultimately gets the best of them. Whatever fails to be captured by sticky cannabis stigmas falls to the ground from where, as we have seen, the pollen grains can be unearthed thousands of years later by eager botanists and archaeologists. As soon as the female flowers are pollinated, they cease secreting cannabinoids and switch all their energy into producing hundreds of thousands of fruits, strictly named “achenes” but informally called “seeds.” So, if you’re growing hemp for seeds, having male flowers around is fine. But when you’re cultivating cannabis for medicinal or intoxicating cannabinoids, then male plants are public enemy number one and must be culled. Depriving the female plants of male pollen in the botanical equivalent of a nunnery encourages them to up the production ante. Unlike nuns, and acting more like desperate Tinder users swiping indiscriminately to find a mate, the female flowers increase their numbers of stigmas and sticky resin. Ultimately this process runs out of steam, and the plant is left at each branch tip with a fat unfertilized flower bud, or cola. Every bud is packed full of red-brown deceased stigmas and sprinkled with a frosting of sticky, shiny cannabinoid-rich crystals. This familiar nugget is known as “sinsemilla,” Spanish for “without seeds.”

Unlike cannabis growers, hemp farmers don’t give a fig about buds, to mix botanical metaphors. They grow male and female plants together but harvest everything early, before the pollen disperses, so that the desirable fibers are not degraded post-fertilization. Or they avoid mowing a portion of the field to let fertilization do its thing and hemp seeds to develop for next year’s crop.

Nobody really knows why the female flowers produce resin. One hypothesis is that it protects the female flowers from drying out in hot dry climates, where cannabis resin production is maximized. Traditionally, this is where drug-bearing strains have been cultivated. Resin is not secreted after the fruits have ripened.

Drug and hemp varieties are presumed to share a common origin but over millennia have been driven to diverge by farmers employing different cultivation approaches.[15] These differences in cannabis plants draw us inevitably into a botanical discussion. For years cannabis horticulture has been the province of hands-on growers more concerned with practicality than accurate terminology, to the detriment of the latter. For example, the term “bud” to cannabis consumers and growers refers specifically to a cluster of female marijuana flowers. To botanists, however, this is a far less specific label that designates any newly appearing bump that signals an emerging plant part of any type from leaf to twig.

Humans have been successful in consciously tinkering with nature and trying to improve selected wild living things for human benefit. We’ve tamed the friendliest wolf cub in the pack, bred the cat that’s the best mouser, and propagated the corn plant with the biggest kernels. Or like the Duke of Bedford, bred the fattest cattle. Thus, our species has kept the undesirable wolves from the door (and the new domesticated ones inside) and the greedy rats out of the better, plumper crops. Selective plant breeding in particular goes back thousands of years. Wine grapes, corn, peppers, tomatoes, tobacco, potatoes, and more recently ornamental plants have all thrived under our attentions. Michael Pollan describes much of this process masterfully in books such as *The Botany of Desire*.[2] As he points out, marijuana crops have been historic beneficiaries of such human attention. We have selected desirable features such as plumper seeds, stronger fiber, or more potent psychoactive properties. More recently we have imbued many fruits and vegetables with characteristics appealing to supermarket consumers. And in our past lives as hunter-gatherers, we’ve capitalized on the novel characteristics in random genetic mutations or “sports” that Nature occasionally throws our way. This makes sense: no primitive agriculturalist wants to be the tribal farmer responsible for providing a pitiful crop of tiny hemp seeds that fails to tide the group through a freezing winter. Equally undesirable is the subpar shaman doling out low-grade schwag in place of powerful insight-inducing weed at an important religious ceremony. (Exactly how shamans tested for cannabis potency ahead of time leads to interesting speculation, but I’m sure there was never a shortage of eager volunteers.)

When and where was cannabis first used for its mind-altering properties?

Part of the answer to this question relies on ancient texts and later retrospective reports of ancient practices. Until recently, questions regarding the earliest use of marijuana as a psychedelic led to much speculation but few definitive answers. If archaeologists discover a handful of ancient hemp seeds, without more evidence it’s hard to tell whether the associated plants were used as a seed crop, grown for their fiber, or grown for medicinal and psychoactive properties. Surprisingly, even during the period of time that I have been writing this book, archaeology has been filling in the gaps with scientifically convincing physical evidence. Discovery of

such evidence beats the odds, given the challenge of preserving archaeological traces of cannabis-use activities or even plant samples whose THC can be analyzed.

According to John Chasteen, the Indian Atharva Veda manuscript mentions ceremonial use of the bhang plant three thousand years ago, in a context suggesting intoxication—that is, alongside mention of the sacred (but currently unidentified plant species) soma. Thereafter, written texts from India are spotty and relatively uninformative for literally thousands of years, until the early 1300s. Chasteen suggests this absence can be explained in part by the fact that much early literature was written on palm leaves, which decay in the hot, damp Indian climate.[15]

Just over 10 years ago, among the Yanghai tombs in the Turpan district of Northwest China, in the Xinjiang desert region to the north of the Pamir Mountains, a large amount of cannabis plant material radiocarbon-dated to 2,700 years ago was discovered in the tomb of a Caucasoid male in his mid-40s. The man is assumed to have been a priest or shaman of the Gushi culture, based on artifacts found in the tomb such as a rare and distinctive harp. Almost a kilo of chopped and pounded cannabis was buried next to the shaman's head and feet in a large leather basket and wooden bowl. Because of the deep burial and "old and cold" climate conditions, the cannabis was superbly preserved.[16,17] According to Professor Ethan Russo, these cannabis remains consisted almost exclusively of the more psychoactive parts of the plant, with the large stalks and branches removed. A multidisciplinary international team confirmed the identity of the cannabis through botany, plant chemistry, and DNA analysis. They showed that the botanical remains contained significant amounts of THC. The still-green plant material, unusually well preserved in the dry, cold Gobi Desert environment, was immediately identifiable as cannabis. Even the characteristic glandular trichomes were still obvious, along with the distinctive seeds. The latter were plump, characteristic of cultivated rather than wild cannabis. Nothing in the tomb betrayed how the cannabis might have been consumed.

Separately, in a burial site excavated in 2015, an even more startling discovery was made in the 2,400- to 2,800-year-old Jiayi tombs (also located in the Turpan region). This ancient cemetery had been discovered by chance when Chinese workers cleared an area close to an ancient riverbed, ironically to construct a new graveyard. In all, 240 tombs were excavated, with the area yielding ceramic pots, bows and arrows, and bones of domesticated animals including horses, goats, and sheep. In only one of these tombs, the archaeologists found something truly unexpected. Surrounded by red-colored earthenware pots and lying on a bed made of wooden slats, with his head resting on a reed pillow, a 6-foot-tall man in his mid-30s had been buried. A bouquet of 13 cannabis plants was spread diagonally across his upper body like a shroud. Due to the dry climate, the 2- to 3-foot-tall plants were easily identifiable, although they had turned yellowish brown. All were locally grown female cannabis plants bearing newly ripe seeds. The plants still had roots attached, and a microscopic view of the buds confirmed the

presence of densely packed golden-colored glandular trichomes.[18]

The story continues. In 2019, archaeological and biochemical collaboration revealed the earliest chemical evidence to date of human psychoactive use of high-THC cannabis via smoking and told us definitively for the first time how the cannabis was consumed.[19] The plants in question were cultivated and used in funerary rites 2,500 years ago in central Asia, as shown by a cemetery excavation that took place at the foot of the Pamir Mountains in Northwestern China. This region is located 10,000 feet above sea level, in the area known as "the roof of the world," near the China-Tajikistan border. The cannabis chemical remains found at this Jirzankal burial site bore high levels of THC, as shown by gas chromatography–mass spectrometry (GC-MS), the technique that we encountered in Chapter 1. The plants and their associated artifacts were excavated from ancient circular graves, having been buried under rounded mounds and surrounded by rock borders. Among the skeletons were interred harps and pieces of silk. Fascinatingly, 8 of the tombs housed a total of 10 ancient charred, bowl-like wooden burners carved from logs. Each contained ping-pong-ball-sized stones that had obviously been exposed to fire. Beijing scientists analyzed material from these partially burned wood braziers and the stones. They detected not only CBD but more importantly cannabinol, a unique chemical byproduct of heated and air-exposed THC. The cannabinol was much more highly concentrated than in most ancient wild hemp samples and there was much more of it than any previously discovered at an ancient site. This implied that the plants had been bred specifically for psychoactive purposes. The analysis isn't able to tell us precisely how much THC was in the original long-since-vanished cannabis plant material, only that it had to have been at levels much higher than that found in wild hemp. The authors speculated that the bulked-up THC levels could have been produced in response to environmental stressors such as higher levels of UV light, sunshine, or high altitude. All these conditions boost THC levels in modern-day cannabis.

How do these clues fit together? Inferentially, fire-heated stones had been dropped onto high-THC herbal cannabis material (or vice versa) to produce intoxicating smoke that was inhaled by the mourners, perhaps inside small tents to confine the smoke. The artifacts found at the site are fairly typical for practitioners of the ancient Zoroastrian faith that originated in Persia, versions of which still persist today. Mark Merlin, professor of botany at the University of Hawaii and coauthor with Robert Clarke of the massive *Cannabis: Evolution and Ethnobotany*,[20] stated that this discovery "adds to growing indications of an association among many cultures of cannabis with the afterworld and death . . . [and that cannabis was] used to facilitate the body communicating with the afterlife, the spirit world." [21] The harps suggest that music was used as part of the funeral ritual. The obvious connection between weed, music, rock, and the Dead was also made in a *New York Times* article.[22]

Even though this discovery is the earliest archaeological evidence documented to date, it certainly is not the last word on whether this particular geographic area was where the practice began. The flat plain below the Pamir Mountains where the

cemetery is located is right on the Silk Road. This route formerly connected trade and travel from Central and Southwest Asia with China. Ritualistic use of high-THC cannabis is speculated to have started even earlier in regions from Syria to China. Perhaps the practice spread alongside exchange of religious and cultural ideas and customs, along with trade goods (including crop seeds), up and down the Silk Road. Convergent evidence of cannabis use in this period derives from ancient graves elsewhere in China. Hemp was first used in China twelve thousand years ago or more for fiber, and cannabis seed was a staple grain in the region from ancient times. The pictographic representation of cannabis ("ma") is easily recognizable as a depiction of stalks of hemp hanging upside down in a shed to dry. The Chinese recognized that the plant grew in male and female forms and that male plants were superior in providing fiber, while the females were preferred for intoxication. For the latter, there are various descriptions of how to prepare the plant, dating back to the 3rd century BC.

While the scientist/nerd part of me is fascinated by the archaeological details of cannabis in Pamir funeral rites, my inner psychiatrist wants to know what the mourners at the time of this ancient funeral actually thought and felt as they took a hit of cannabis vapor from the smoking, terpene-rich juniper-wood brazier. Presumably the ritual helped them contact a parallel spirit world where they could commune with the gods of nature and the dead person's soul. The ritual chanting and music combined with the cannabis may have helped shape their thoughts and feelings of grief at losing an important member of the community, as well as aiding some form of communication with the deceased.

The general outline of my speculations on funeral rites squares roughly with the one ancient historical account of ceremonially inhaled cannabis recorded by the Greek historian Herodotus (known as the Father of History). Written around 450 BC, this description occurs in his account of the Scythians (a group of Central Asian tribes that lived beyond the Araxes River). This roughly 700-mile river in the Caucasus begins in Turkey and runs through current-day Armenia, Azerbaijan, and Iran, coincidentally close to the Azerbaijani city of Ganja. Herodotus detailed how the Scythians sought an altered state of consciousness as a communal experience using cannabis, a plant whose appearance he describes, remarking that it both grows wild and is cultivated. He relates vividly how the tribe would kindle a bonfire, toss on cannabis, inhale the smoke to the point of intoxication, dance, and burst into song. He also relates that in a purification ritual following a burial, the Scythians cleansed themselves, then leaned three poles against one another around a dish and draped the frame with felted woolen blankets. Next, red-hot stones from a fire were placed in the dish, cannabis seeds tossed onto the glowing stones, and the Scythians crawled under the blankets to inhale "the dense smoke and fumes . . . causing them to shriek with delight." [23] This latter description of enjoyment doesn't imply that the cannabis was being used recreationally and separately from the funeral rites. Anyone who has been to a traditional wake will understand that the phrase "celebration of the deceased's life" can have a quite literal meaning.

The accounts of Herodotus jibe remarkably well with our current understanding of the Scythians and recent archaeological evidence of their use of cannabis. These nomadic peoples were groups of Eurasian Steppe-dwelling herders, who controlled huge areas of land all the way from Siberia to Eastern Europe. They were skilled horsemen, archers, and crafters of strikingly beautiful jewelry. Because of their nomadic lifestyle, they left behind no cities or permanent settlements. The tribe traveled and traded widely between China, the Middle East, and Eastern Europe from as early as the 9th century BC over an era lasting 1,200 years. They also held elaborate funerals and buried their deceased nobility in large elaborate mound-like tombs.

From one of these structures—a frozen burial mound in Pazyryk, located in the Altai Mountains of Siberia close to the Mongolian border, dated somewhere between the 5th and 3rd centuries BC—early 20th-century archaeologists unearthed a variety of objects. These included a frame made of wooden poles that once belonged to a small tent and a copper-and-bronze cauldron, or censer, containing burned hemp seeds and stones dated to around 2,500 years ago.[24] Close by was a fur-lined leather bag filled with cannabis seeds and clothing made of hemp. The tent frame presumably belonged to a long-vanished cannabis inhalation tent exactly as described by Herodotus. Later, in 1970, another archaeological group excavated a leather Scythian flask containing hemp seeds. They asserted that smoking cannabis may have been part of everyday life, not merely a funeral rite. Those seeds were minute and marbled, resembling tiny turtles. They were also consistent with observations of wild cannabis strains made by Nikolai Vavilov, an early 20th-century botanist, and conclusions made from recent agronomic analysis.

More recently, in 2013, Andrei Belinsky excavated a 2,400-year-old Scythian tomb that contained golden artifacts, including exquisitely detailed gold vessels portraying violent images. Inside the vessels were sticky residues that local scientists confirmed contained cannabis and opium.[25]

For years, people have tried to convince me that the Bible mentions cannabis. “Check out Exodus 30:22–29,” they say. “A key ingredient in the recipe for sacred anointing oil is ‘kaneh-bosm’—cannabis, get it?” Usually I’d greet these statements with a tolerant smile, secretly thinking this was a typical stoner myth, along the lines of “George Washington smoked weed, and the Declaration of Independence is printed on hemp paper.” But in May 2020, the *Times of Israel* newspaper announced that two researchers from the Israel Museum in Jerusalem had just published an academic article in Tel Aviv University’s Institute of Archaeology journal. The investigators had analyzed residue scraped carefully from two side-by-side Biblical-era (760–715 BC) altars in a shrine excavated at Tel Arad. (This site is located in southern Israel, about 25 miles west of the Dead Sea.) Careful chemical analysis revealed one altar contained a mixture of cannabis (THC and CBD), along with unspecified animal dung. The larger companion altar contained traces of frankincense and animal fat. The team of archaeologists and scientists believed that the cannabis was used as a psychoactive substance

intended to “stimulate ecstasy” in Israelite worshippers. Why animal poop, you’re probably asking yourselves? Dung burns at a relatively low temperature, sufficient to release THC without burning everything up. Conversely, animal fat burns hot, and high temperatures are needed to evaporate frankincense.[26] As researcher Dvory Namdar told a reporter from the Israeli newspaper *Haaretz*, “To induce a high you need the right temperature, and they clearly knew this well, just as they knew which fuel to use for each substance.” [27] So, jokes about “high priests” and “Jewish high holidays” aside, this archaeological find seems to confirm that “kaneh-bosm” was in all likelihood actually cannabis. Also, this discovery represents the earliest documented instance of marijuana use in the region. If you are curious to learn more about the topic of marijuana in the Old Testament and its role in Judaism up to the current day, I recommend the book *Cannabis Chassidis: The Ancient and Emerging Torah of Drugs (A Memoir)* by Yosef Leib (Ben Yehuda Press, fourth edition).

How do we classify different kinds of cannabis plants?

The question of how to classify cannabis is inextricably linked to techniques for growing the plant: a case of horticulture meets nomenclature. In our modern age of dispensaries and selective marijuana propagation by cloning, we’ve retained and updated many of these ancient plant-breeding principles. Unfortunately, alongside the ancient business of producing ever-better weed, we have added a lot of unnecessary perplexity to the process. This includes confusing and misapplied terminology. Everyone from breeders to budtenders chats knowledgeably but often imprecisely about the nugs in question. Back in the 1970s, the Firesign Theatre comedy troupe released an album entitled *Everything You Know Is Wrong*. This is an apt summary of the befuddled world of cannabis classification. Let me show you why. Many people, even seasoned marijuana consumers, speak about “varieties” and “strains” of cannabis. Walk into the average dispensary and you will see listed for sale a selection of “strains” with exotic names such as Blackberry Kush, Blue Widow, Sour Diesel, Super Lemon Haze, Girl Scout Cookies, Purple Kush, and Lamb’s Bread. Dispensaries sell “varieties” with an assigned name such as Rainbow Gummeez and some basic information; for example, “Indica strain; 15% THC, 5% CBD, has energetic effects.” What’s wrong with this picture? First of all, “strain” is not a valid botanical term. Second, the boundary between *Cannabis indica* and sativa has been blurred by plant breeding to the point of obscurity. Third, we often don’t know exactly who is using what kind of assay to come up with that “15% THC” figure. Fourth, what subjectively makes one person feel “energetic” may well make another sleepy, or paranoid or anxious. (Our Holi narrative made that point.) And finally, are the Rainbow Gummeez buds I’m purchasing from dispensary A the same as those I bought three months ago from dispensary B?

The bottom-line question is what useful information do we need to distinguish a nugget of Three Bears from one of Acid Rain? And what’s the correct

terminology we should be using to pose this question? To address these important issues, we will need a botanical detour to explain the differences between strains, species, cultivars, landraces, chemovars, and varieties. My apologies if your head is soon whirling and buzzing from fact overload before you even take a toke of the weed we are talking about.

In the biological world, the term "species" refers to individuals that can reproduce sexually with members of the same species and their progeny in turn can also reproduce sexually and produce offspring, or what my friends south of the Mason-Dixon line refer to as "chirren." For example, horses and donkeys are related but separate species that can mate to produce mules, but mules are sterile. Lions and tigers are another example of separate species that can mate and produce "tigons" or "ligers." But when tigons mate with each other, they are unable to produce offspring. All three types of cannabis, indica, sativa, and ruderalis that we encounter below easily cross-pollinate, producing viable plants that are a mixture of the different types and that easily produce viable seeds themselves. So if I had to choose, I'd agree with John Chasteen that different groups of farmers have created separate varieties over the years, from a single original species, by selecting for separate features of ancestral cannabis, whether long, tough fiber, buxom seeds, or plump resin-rich flower buds. Sixties-era hippies and their plant-breeding successors have blurred the lines even more by crossing varieties to boost THC. If you concentrate on developing a breed of chickens that are productive egg layers, they are unlikely to be terrific meat producers. Thus, cannabis varieties bred to be high in THC are generally low in CBD. This changing ratio has health consequences relevant to psychosis, as we'll explore a little later. Although historically species of all sorts were initially described by exact appearances, classification now relies on chemistry, genetics, microscopy, and other techniques and branches of science, as we will see.

The species *Cannabis sativa* (fancy Latin for cultivated cannabis) was initially described by Leonhart Fuchs, the German physician and founder of modern botany, in 1542 in his classic book, *The New Herbal*. Fuchs is commemorated in the naming of the plant and color fuchsia. The dual moniker of *Cannabis sativa* was adopted by the Swedish botanist and physician Carl Linnaeus in his exhaustive list of plant species' descriptions in 1753 to describe the European hemp plant. Thirty years later, Jean-Baptiste Lamarck, French soldier, biologist, and plant nerd, described *Cannabis indica* as a possible distinct species originating in the Indian subcontinent, differing in being shorter and bushier than *Cannabis sativa*, with broader leaves. Finally, we encounter the Rodney Dangerfield of the cannabis world, a species that many botanists claim doesn't really exist, *Cannabis ruderalis*, often insultingly referred to as "ditch weed." Ruderalis was named by the Russian botanist Janischewsky in 1924, when he discovered a "new" noncultivated wild cannabis plant. The term "ruderal" derives from the Latin word for "rubble." Ruderal plant species colonize land after it's been cleared. These quick-fire opportunists are generally tough, scrubby plants, matching their role as hardy botanical pioneers. There has been an ongoing battle of the plant classifiers,

with some advocating for a single cannabis species and others for distinct and separate species.

How then can we settle this botanical bickering and definitively classify the plant? Classically, cannabis varieties are named by morphology. Indica plants are short and squat with big leaves and wide leaflets, and are favored by indoor growers due to their short six- to eight-week life cycle. By contrast, sativas are tall and narrow-leaved, and reputed to have stimulating and cerebral properties. Cannabis consumers speak knowledgeably of differences between indica and sativa parsed by their subjective psychoactive effects (such as body high, sedative, couch lock). These designations are used widely in dispensaries, by users, and online, including, for example, by Healthline.[28] Logically we could perform this distinction using a plant's outward appearance but, as a reminder of the potential limits of classification by morphology: Danny DeVito and LeBron James do not belong to different species. A second method to distinguish species might be by place of origin, but this remains pretty much lost in the mist (or smoke) of history. Additionally, the plant has been so extensively crossbred that the botanical cat's cradle of different types is almost impossible to disentangle so many years down the line. Ancestral forms have likely long since disappeared and may no longer even exist in the wild, as the landrace-seeking hippies of the '70s discovered. Examination of the genes of multiple sativa and indica "strains" clearly shows this blurring. Yet another way to classify the plant might be through its effects, either subjective ones (for example, sedative, activating) or its medicinal properties—for which we would ideally need clinical trials. But here we would have to account for the fact that different people may have different subjective responses to the same cannabis sample. Another approach might be to use genetics and to describe the key genes determining various types of vital plant characteristics, from the shape of its leaves to the amount of THC it can manufacture. (More on these genetic topics a little later.) Chemistry too plays a role in classification, for example in distinguishing THC to CBD ratios.

"Strain" is the term used correctly by microbiologists to describe bacteria and incorrectly by some cannabis breeders and dispensaries to describe varieties of the plant. In the movies when you see a white-coated scientist take a wire loupe, poke it into a bacterial colony, and then swish it across the face of a virginal petri dish to grow a new colony, "strain" refers to what they're endeavoring to multiply in the growth medium. In this context, a "strain" is defined as the descendants of a single bacterium. This term is not employed in botany but used casually to refer to variations within cultivars and their offspring. So we can cross "strain" off our list of terms to ID cannabis varieties.

"Variety" on the other hand is a bona fide term. It refers to the unique characteristics of a plant that occurs in nature. Plant varieties are cultivated, or "bred." by humans, in a process that involves selecting deliberately for particular traits, such as larger flower buds, more attractive flowers, more robust plants, and so on. The potato varieties that reach your local McDonald's have been bred precisely for large size and optimal starch content. The process of creating new

varieties also relies on sharp-eyed plant breeders deliberately picking a “sport” (the name for an unusual plant that appears randomly in nature by genetic mutation). New varieties also arise by hybridizing two plants with distinguishing features and breeding them into a new entity that marries their two desirable characteristics. Examples might be taller plants with bigger flower buds. Although true varieties produce comparable copies of themselves when their resulting seeds germinate, hybrids may not.

In plant and animal biology, a “hybrid” is the offspring that results from genetic mixing: when two organisms of different breeds, varieties, or species that have different qualities are combined through sexual reproduction. Hybrids may display the different qualities of each parent, a blend of both, or even exhibit new qualities such as “hybrid vigor,” where the offspring is bigger or tougher than either parent. Hybrid vigor is a guiding principle in animal breeding. Hybrids such as cockapoos (cocker spaniels mated with poodles) are sometimes referred to as “designer crossbreeds.” But there are large elements of trial and error, and even pure blind luck, in creating a successful hybrid. Supposed hybrids of indica and sativa, such as White Widow, are generally described based on approximate proportions of their parents (such as 60% indica, 40% sativa) and by definition are said to exhibit traits from both. The hope is that hybrids co-mingle the desirable parental traits. But as any plant breeder will tell you, that doesn’t necessarily occur. A classic illustrative example of an unfavorable hybrid from outside the plant world is of the proposed pairing of George Bernard Shaw, the homely Dublin-born Nobel Prize–winning playwright, polemicist, gadfly, political activist, and cultural critic, with Ellen Terry, the classically beautiful, accomplished, and notably histrionic actress with whom he had a lengthy correspondence. Apocryphally, Terry suggested they have a child together. “You have the greatest brain in the world, and I have the most beautiful body. Just think of it, we will produce the most perfect child.” Shaw, in his curmudgeonly way, responded with “Yes, my dear, but what if it inherits your brain and my looks?” [29]

Back to cannabis breeding. Commercial cultivars often use “auto-flowering” plants that automatically switch from vegetative to flowering stage with the plant’s age as opposed to ratio of dark to light hours, as occurs with “photo-dependent” strains. In nature, indica and sativa cannabis plants switch to flowering as summer changes to autumn, and the ratio of light to dark hours approaches one. Cannabis growers need to fuss with lights to force buds to appear at the right time. Crossing or hybridizing ruderalis with these other varieties is common because, uniquely, the ditch-weed flowers develop independent of photoperiod, propelled only by the plant’s maturity. To create the original hybrid, you only need pollen from a male plant to fertilize the female. Ruderalis is thus used to breed auto-flowering varieties. These days, commercial crossbred hybrids are usually a mixture of all three cannabis types and are both auto-flowering and fast growing. Male plants are excluded from groweries to obtain resin-rich sinsemilla.

More botanical terminology. In contrast to simple varieties, “cultivars,” short for “cultivated varieties” (sometimes termed “varietals”), are plants purposely

selected for their desirable characteristics. Unlike varieties, seeds of a cultivar produce plants that differ from the parent. Leaving things to chance is usually a bad bet when you're starting off with something good whose desirable traits you want to preserve. Thus, profitable cultivars are bred true to the parent by a series of methods that include propagating cuttings, cloning, grafting, or tissue culture, all of which are employed in marijuana cultivation. Such procedures, as we encountered in the Colorado growery, produce exact copies of the parent plant through a method other than seeds. Essentially, cultivars originate from nurturing various-sized pieces of the parent plant to produce precise copies, or clones, of themselves. In the animal world, Dolly the sheep was a famous clone. Cannabis breeders are not a particularly risk-averse group. But given the vagaries of propagating a successful variety once you have put so much time and effort into creating it, making generations of numerous exact copies is achieved most predictably by taking cuttings from the mother plant and propagating the resulting clones. Carefully tended, mother plants can be wheedled into surviving way beyond their designated annual lifespan. When clones mature, an important question for growers is how to name your resulting babies in order to market or "brand" your products. Most often they are given catchy titles, whose purpose is to telegraph key descriptive information such as size (big bud), color (rainbow, purple train wreck), supposed geographic origin (Kush, Hawaiian), smell (sour, diesel, lemon, skunk), or taste (pineapple, strawberry). But to benefit fully from the fruits, or in this case the buds, of your plant-breeding labors, cultivars must be legally registered. Large garden-plant nurseries do this regularly. Because cannabis is illegal in most jurisdictions, currently this registration of cultivars almost never happens. Using these definitions, it should now be clear that a cannabis plant can be both a variety and a cultivar.

This chapter has provided some key information on where and when cannabis evolved, archaeological hints as to when it began to be used for intoxicating purposes, and schemas for classifying the cannabis plant botanically. But we will learn the essentials of how cannabis synthesizes intoxicating and other cannabinoids and terpenes, and how to further classify the plant chemically and genetically in Chapter 8.

Chapter 4

NEUROSCIENCE

> These compounds serve as a new and additional class of endogenous signaling molecules involved in a plethora of physiological functions.
>
> D. CHANDA, D. NEUMANN, AND J. F. C. GLATZ, "The Endocannabinoid System: Overview of an Emerging Multi-Faceted Therapeutic Target," 2019[1]

> Your body is teeming with weed receptors.
>
> M. SCUDELLARI, *Scientist*, 2017[2]

This chapter covers some key aspects of how the psychoactive constituents of cannabis interact with our brains to produce the characteristic experiences associated with the drug's "high." Beyond that, I will explore the body's complex and naturally occurring neurochemical internal cannabinoid signaling system that interacts with plant-produced chemicals found inside the cannabis flower. This so-called endocannabinoid system (ECS) inside of our brains and immune cells has important but complicated interactions with other brain signaling systems. We will challenge the idea that cannabidiol (CBD) is not psychoactive, and explore what pharmaceutical companies are doing in terms of designing drugs to make the brain's cannabinoid system behave in finely tuned ways for therapeutic purposes. We will also investigate how rogue Chinese chemists design super-chemicals to coax the same system into producing super-highs.

Revelation number one. Imagine that 50 years ago explorers suddenly stumbled upon a vast lost continent, populated by people who spoke languages similar to our own and whose culture paralleled ours, but whose entire existence had been previously completely unsuspected. This discovery sparks a wave of investigation by geneticists, linguists, geographers, behavioral scientists, and research investigators of every stripe seeking to understand every detail of this mysterious land and its puzzling populace. After a period of intense study, scholars feel pretty confident that they have all the details straight, the key measurements complete, and that they comprehend the major facts and interrelationships. Basically they have everything pretty much figured out. Revelation number two. Now imagine that these investigators gradually realize the rules that govern the new land are significantly more complex, bizarre, and contradictory than anything in their prior experience. Principles that apply in one part of the territory have corresponding counterexamples nearby. Many of the scientists' early predictions about the continent turn out to be incorrect, initial expectations are confounded, and they

come to the realization that what they once believed they knew was simplistic and undermined by contradictory evidence.

This little fable encapsulates the unexpected discovery of the complex and ubiquitous endocannabinoid system 50 years ago, by a scientific team seeking to understand only how marijuana makes us high, and our subsequent attempts to delve into the system's underlying neuroscience. The more research that is undertaken on this network, the more byzantine, contradictory, and convoluted its details appear to be. Telling this story necessarily contains a fair number of technical details. But part of the narrative also includes tales of scientists traveling on buses with shopping bags stuffed with large chunks of Turkish hashish, and details of black truffles, spiny puffer fish, mutant rats, peanuts, sea squirts, and volunteers getting buzzed in research labs. So stay with me for the ride.

How the brain works

In order to understand questions such as how marijuana gets us high and how CBD and THC exert their medicinal effects, we need some basic understanding of both the body's ECS and how the human brain operates. That's a tall order and involves some rather complicated biology, but let's give it our best shot, starting with the brain.

The human brain is probably the most complicated and elusive thing in the universe. Explaining how it works is an enterprise that remains mostly unsolved and that has preoccupied some of the finest scientific minds (or brains) for centuries. Nobel Prizes have been awarded and lengthy research careers devoted to this topic without yet really grasping many of the fundamentals. Given all of that, let's boil this entire massively convoluted topic down to a two-minute elevator pitch that ignores all the complexity and subtlety of this magnificent organ. We will focus on just enough of the small-scale details to help us grasp the essential features of the ECS.

At its core, the brain exists to provide us with accurate information about the outside world for the purposes of guiding our behavior, filing away accumulated experiences and knowledge in memory and anticipating the future. Take these examples: that stripy buzzing insect over there gave me a nasty sting last year; I'd best avoid it. Or, my wife's birthday is next week. I'll need to buy a nice card on the way home tonight. The basic starting point for all these complicated perceptions and behaviors are nerve cells, or neurons, the simplest units of brains and nervous systems, whose purpose is to pass along and integrate little packets of information. This information may come from the outside world, for example, provoked by sounds or images, or from inside the brain itself in terms of memories, thoughts, and feelings. Nerve cells come in different shapes and sizes, but the typical neuron resembles a child's drawing of an octopus, with one super-long tentacle (called an "axon") that ends in a tuft of branches that connect with other neurons. In the biggest neurons, the part that looks like the octopus's squishy body and contains the nucleus (named the "cell body") can be as big as one-tenth

of a millimeter across, with the teeniest ones being almost a hundred times smaller. From the cell body, a series of mini-tentacles (named “dendrites”) poke out. These are the means by which the cell receives input from other neurons. The disproportionately long axon tentacle, which is the main unit to conduct nerve signals to other neurons, can be anywhere from a few millimeters to several feet in length. The billions of nerve cells in our brains form trillions of possible connections and communicate with one another through electrical impulses that have an underlying chemical basis. This communication happens across tiny gaps between the neurons (called “synapses”). Nerve cells are excitable, not in the Warren Zevon sense, but because they are specialized in generating, modifying, and passing along fast-traveling electrochemical pulses akin to coded signals. Neurons are primed to fire these electrical charges because little molecular pumps inside them are constantly transporting electrically charged particles, such as potassium ions, in and out. This process prepares the cell to discharge electrically when triggered by specialized chemical compounds (known as “neurotransmitters”). The “happy hormones,” which are actually not hormones, dopamine (DA) and serotonin are two perhaps familiar examples of the more than two hundred known neurotransmitters produced by our bodies that act as molecular messengers between nerve cells. Their release from one nerve cell into the synapse causes a wave of nerve impulses to leap to another neuron. This results in the latter either firing or switching off the electrical signal. When and how often the neuron fires codes information that it passes along down the chain. If as a child you were bored by *Sid the Science Kid*, uninspired by *Mr. Wizard’s World*, suffered ennui with *Bill Nye the Science Guy*, or became carsick on *The Magic School Bus*, you may want to skip the next several fact-packed paragraphs and dive straight into the ECS discussion. Otherwise, bear with me.

Neurotransmitters are released from secure stores in tiny sacs inside the neuron on one side of the synapse, where they have usually been synthesized from amino acids. The name dopamine (dop-*amine*), for example, indicates that origin. This compartmentalized storage is necessary so that the transmitter chemicals don’t leak out and cause neurons to fire randomly. Rather, their release is usually provoked by a prior electrical signal. The direction of this signal transmission is usually one-way from a pre-synaptic originating neuron on one side of the synapse to a post-synaptic target neuron on the other side, and so on down the chain. Numerous targets for different neurotransmitters may exist on the surface of a given neuron, allowing the cell to respond to and integrate incoming information from many sources before deciding whether or not to fire. In general, there are specialized neurotransmitter receptors on the post-synaptic neuron to which specific neurotransmitter molecules bind. These docking sites are also highly specific. Thus the shape of a particular neurotransmitter allows it to fit precisely into its dedicated receptor like a tiny distinct chemical key into a personalized lock. The neurotransmitter “key” is referred to as a “ligand” because it binds to the receptor. This term stems from the same Latin root word that gives us names of things that bind, including ligatures and ligaments. The receptor “locks” sit on the

post-synaptic cell surface and are often configured in the form of so-called G protein-coupled receptors (GPCRs). Such proteins detect specific transmitter molecules. In response, they activate signaling pathways inside the cell, acting like molecular switches (or, if you prefer, given their G-protein basis, tiny G-spots). GPCRs of one sort or another are biologically critical. They are targets for example for over one third of all FDA-approved drugs. GPCRs perform this function by being woven snakelike through neuron-cell membranes, simultaneously touching both the cell's inside and outside. When a ligand binds to its unique GPCR, the latter changes its three-dimensional shape. This temporary modification makes it less of a lock or docking site for the transmitter and more of a mini-machine that triggers a cascade of chemical changes inside the post-synaptic neuron. A ligand that binds to a receptor and switches it on or activates it is called an "agonist" at that particular site, from the Greek word for "contest." Logically, a ligand that fits into the same lock and blocks an agonist's effects is termed an "antagonist." Likewise, a ligand that binds to the receptor and activates it weakly, in a half-assed way compared to a full agonist, is called a "partial agonist." As soon as their signaling duties are done, neurotransmitters are quickly whisked away from the scene of action at the synapse.

Once acted on by a neurotransmitter ligand, post-synaptic neurons are connected to yet other neurons (typically via several thousand synapses) so that the electrical message gets passed on like a baton in an information relay race across the brain. Over time, synapses that are frequently activated work faster and more efficiently so that, in a very basic way, they can "learn." From this simple, basic arrangement of neurons, one can imagine scaling everything up into something more brain-level in nature. Remember that these nerve cells may be metaphorical building bricks of the brain, but unlike bricks they are dynamic and ever-changing. Throughout development, groups of neurons within the brain that perform similar functions or contain specific neurotransmitters organize to form complex circuits and systems. In turn, these circuits are themselves components of hierarchically organized metasystems. Thus, when the brain is called on to perform a particular task such as recognizing an object or remembering a fact, the relevant modules of neuronal architecture coordinate with each other across different regions most effectively to get the job done. The whole arrangement is underpinned by millions of coordinated neurons acting in synchrony.

An apology is in order at this point. My use of words such as "usually" and "typically" above is a prelude to confessing that the ECS, both inside and outside the brain, confounds many of the rules of neurotransmission that I just laid out. For example, the relevant ECS neurotransmitters are built from fats, not amino acids. They are not stored long-term in tiny sacs but synthesized on the fly as needed. Their direction of transmission is backward compared to the usual one. And while there are specific receptors for cannabinoids, there are no unique, specialized cannabinoid neurons like those that exist for DA or serotonin.[3] Finally, so far we've only got as far as revelation number one: like the eager explorers I mentioned above experienced, there are many more nuanced ways in which the

ECS will reveal itself as utterly novel.

What is the endocannabinoid system?

So, you are probably asking, what's the ECS and what's going on under the hood here? The general term "endocannabinoid system" refers to the whole kit and caboodle of cannabinoid neurotransmitters manufactured in the body, the specialized receptors they lock onto in the brain and elsewhere in our anatomy, and the many enzymes and proteins that synthesize, transport, and break them down. Cannabinoid neurotransmitters that we will meet in a moment, such as anandamide, are unique in being fat- (lipid-) based. (Lipids are small carbon-based fatty molecules that don't dissolve in water but in organic solvents like acetone/nail-polish remover and benzene.) Lipids are used as general-purpose molecules all through biology to build cell membranes, to store energy, and, most relevant here, uniquely in the ECS to send signals from one part of the body to another.

In more technical terms, the ECS is an evolutionarily ancient lipid-based signaling system and one example of the type of biological network I described earlier where neurons responding to particular neurotransmitters hang out together in a cannabinoid clique. In this case, the two main cannabinoid neurotransmitter ligands are *N*-arachidonoylethanolamide, thankfully abbreviated to AEA and most commonly known as anandamide, and 2-arachidonoylglycerol (2-AG). Much more 2-AG exists in the brain than anandamide, 10–100 times more in fact.[4] Together, anandamide and 2-AG are known as "endocannabinoids," an abbreviation for "endogenous cannabinoids." This refers to their status as substances found naturally inside (endo) the body and produced there. This distinguishes them from exogenous cannabinoids (exocannabinoids) such as THC and CBD that are produced outside (exo) the body either by plants or in chemical labs. The two endocannabinoids are synthesized in the body from arachidonic acid, a substance that is named for peanuts (arachis), which contain this molecule, and not for arachnids like spiders. Arachidonic acid is an omega-6 polyunsaturated fatty acid that enters our bodies through eating meat and eggs (and peanuts) and is used for important functions like building cell membranes.

Anandamide and 2-AG are neurotransmitter ligands for two distinct types of cannabinoid receptors known unsurprisingly as cannabinoid receptors 1 and 2, abbreviated to CB_1 (cloned in 1990) and CB_2 (cloned in 1993). These two ligands glom onto specific cannabinoid receptors in the typical key-and-lock fashion. CB_1 and CB_2 are GPCRs of the type discussed earlier, located predominantly on neuron-cell surfaces in the brain and peripheral nervous system, and in cells that are part of the peripheral immune system, respectively. The CB_1 receptor protein is built out of a twisted chain of 472 amino acids that weaves in and out of cell membranes seven times, like an intoxicated snake. Researchers have learned how to build mutant CB receptors by altering the chain's building bricks one amino acid at a time, and thereby have determined exactly where THC and (to some

extent) CBD bind to different locations on the CB_1 molecule.

CB_1 is the most abundant GPCR in the brain and central nervous system. This fact is impressive when we realize that 30 years ago nobody suspected that cannabinoid receptors even existed. Cannabinoid receptors are widely distributed throughout the human body. As Megan Scudellari nicely summed it up, "Your body is teeming with weed receptors." [2] Anandamide/AEA binds primarily to CB_1 receptors, where it acts as a partial agonist (refer to the earlier explanation of these). It is also a weak partial agonist at CB_2 receptors. Meanwhile, 2-AG is the ligand for both CB_1 and CB_2, where it is a full agonist. CB_1 receptors are found in especially large numbers in some brain areas such as the hippocampus and cerebellum. Outside of the brain they are also distributed in fat cells and in the pancreas, where they influence metabolism. CB_2 receptors are located mostly in the immune system and certain immune cells. These latter float around in the blood slurping up and neutralizing potentially dangerous microbes and particles. CB_2 receptors are believed to help fine-tune the body's pain responses, and they protect tissues by helping balance levels of immune defenses and inflammation. Much of this information is speculative and still under active investigation. Human CB_1 receptors are coded for by the gene CNR1 (an abbreviation for "cannabis receptor type 1"). They are virtually identical to the rat CB_1 receptor. In contrast, the rodent form of the CB_2 receptor (built by the gene CNR2) is closer to 80% identical to the human one.

THC, the plant-derived cannabinoid (phytocannabinoid), binds to CB_1 receptors, where it is a partial agonist, albeit one that hangs around for a long time, much longer than anandamide with its rapid on/off activity.[1] In this respect, THC is more like the persistent brother-in-law who keeps asking politely but repeatedly whether he can borrow 50 bucks from you and won't take no for an answer. Anandamide and 2-AG are synthesized by a set of enzymes inside post-synaptic neurons. They are broken down by other enzymes, monoacylglycerol lipase (MAGL) in the case of 2-AG and fatty acid amide hydrolase (FAAH) for anandamide, back into arachidonic acid and other simple chemicals.

Endocannabinoid neurotransmitters are produced on demand: when certain post-synaptic neurons fire off an electric current, calcium flows into them, which ultimately triggers the enzyme diacylglycerol lipase (DAGL) to produce 2-AG and a second complicatedly named enzyme abbreviated to NAPE-PLD to synthesize anandamide in these cells. Though the abbreviations MAGL and DAGL (pronounced "maggle" and "daggle") sound like Tolkien's discarded names for *Lord of the Rings* characters, they are found not in underground houses but inside pre-synaptic and post-synaptic neurons, respectively.

These cannabinoid compounds then travel backward to the pre-synaptic neuron to influence its behavior, mainly by stopping neurotransmitter release. Once that's accomplished, they are quickly mopped up by MAGL and FAAH. Anandamide and 2-AG, unlike most plant cannabinoids, are thus both unstable and short-lived. Plant cannabinoids such as THC can have much more long-lasting effects at cannabinoid receptors though, because of that persistent brother-in-law–like

quality. Interestingly, there appears to be a host of additional endocannabinoid compounds in the human body, all of which consist of a fatty acid coupled with either an unmodified or altered amino acid. Most are currently mystery substances whose function is unknown.

Just as some compounds are agonists or activators at cannabinoid receptors, there are corresponding antagonists—that is to say, chemical ligands that bind to the receptor and block its effects. Our bodies don't manufacture these substances. Most such compounds have been synthesized by pharmaceutical companies, with one exception. This is the cannabinoid CB_1 antagonist molecule cannabigerol, synthesized naturally in the cannabis plant. Most cannabinoid antagonists bind to a CB receptor and compete with a naturally occurring endocannabinoid such as anandamide to block its effects. The two molecules duke it out, and the more numerous one eventually gloms onto the cannabinoid receptor. Antagonists are the deadbeats of the psychopharmacology universe. They tend to hang around the receptor and get in the way of the busy agonists that just want to do their job. More recently, pharmaceutical companies have designed compounds active at CB receptors called "positive allosteric modulators," or "PAMs" (like the nonstick cooking spray). CB receptor PAMs latch onto the receptor sites and actually warp the 3D shape and properties of the GPCR so that its usual response to binding a natural molecule of anandamide or 2-AG is magnified. "Negative allosteric modulators," or "NAMs," have the opposite action. They change CB receptor shape so that the usual effect of agonists is diminished. To add a final complication, in this bizarro mirror-image world of receptor antagonists, there is a newly discovered family of "inverse agonists." These molecules block a receptor and reverse its usual activity. Thus, for example, if an inverse agonist binds to a receptor, it will have the exact opposite effect of a regular agonist such as anandamide, rather than merely neutralizing it as an antagonist would. If you find that your head is spinning with all this namby-pamby talk of NAMs and PAMs, inverse agonists and receptor blockers, you'll be gratified to know that there are whole teams of pharmacologists working for commercial drug companies whose entire careers are focused on designing these ECS-modulating compounds as important new therapeutic agents. I have more to say about these scientists, and the drugs they are discovering, a little later.

How was the ECS discovered?

Various cannabinoids, including THC and CBD, were first extracted from cannabis back in the 1940s, but it was unclear which of these chemicals was responsible for cannabis's effects. Early studies suggested (incorrectly) that THC could alter the characteristics of artificial cell membranes. This view became gospel, so that scientists clung to the false hypothesis that the drug worked nonspecifically on the cell membrane to alter cellular characteristics in a broad, unfocused way. People held to that view for a surprisingly long time, until THC's primary intoxicant role was discovered in 1964 by Raphael Mechoulam at the

Weizmann Institute in Rehovot, Israel. Born in Sofia, Bulgaria, in 1930 and forced out of his hometown by the Nazis, Mechoulam emigrated to Israel as a teen in 1949. After training as a biochemist interested in plant-derived medicines, he figured logically that if morphine and cocaine could be extracted from plants and shown to act on specific endogenous brain systems, there might be a parallel story with cannabis. He sweet-talked the local police into giving him 5 kg of confiscated Turkish hashish. (Advice to readers: if you want to score some weed, this is definitely not a recommended tactic.) There is an often-told story of Mechoulam subsequently traveling on the bus back from the police station to his lab with his cannabis-laden shopping bag, surrounded by suspicious passengers curious about the characteristic skunky odor. Together with his colleague Yehiel Gaoni, he was able to extract the component chemicals from this stash, including THC and CBD. One at a time, he then carefully and systematically tested them on animals. Thus the two colleagues determined that THC was the main intoxicant present in the plant. Subsequently they identified the 3D chemical structure of both CBD and THC, and ultimately synthesized both chemicals. Mechoulam remained scientifically active and productive, presenting at cannabis conferences until shortly before his death in March 2023. His research group continues to pursue multiple questions regarding the ECS and the drugs that interact with it. Despite being referred to affectionately as the "OG of cannabis chemistry," he not only didn't inhale but never used the drug himself.[5,6]

Questions still remained, however, as to how exactly THC exerted its effects. Solomon Snyder and Candace Pert had shown in 1973 that brains harbored opiate receptors, but the idea that there might be a specific receptor for cannabinoid drugs was widely discounted. After all, scientists "knew" that it did something or other to cell membranes. Then in 1988, over 20 years after Mechoulam's key paper was published, US scientist Allyn Howlett and her colleague Dr. William Devane conclusively demonstrated that specific receptors for cannabinoids could be detected in rat brains. They first showed that a number of pharmaceutical-company-developed analogs of THC had all the properties of G protein-coupled receptor agonists. Next, they attached radioactive labels to these drugs and demonstrated that the binding sites to which they docked were different from any previously known to pharmacologists. In addition, the radioactive cannabinoid ligands bound to them very avidly and selectively. A few years later, Bill Devane traveled to Jerusalem, where Mechoulam had his lab. Working with a visiting Czech scientist, Devane used pig brains to track down the naturally occurring nervous-system chemical that bound to the newly discovered cannabinoid receptor. (Incidentally, knowing that pigs possess ECS has been exploited recently. Farmers in Washington State have been feeding leftover cannabis stems, roots, and plant trimmings to hogs in order to increase their appetites and enhance their meat flavor.)[7]

Mechoulam nicely summarized everything at the 13th European Congress on Epileptology, where he said, "Receptors don't exist because there's a plant out there. They exist because we, through compounds made in our body, activate

them. So we went looking for the endogenous compounds that activate the cannabinoid receptors." In March 1992, his team isolated the first of these chemicals, a cannabinoid-like substance naturally present in the body. Devane, who had an intense interest in Hindu religion, named it "anandamide," after the Sanskrit word "ananda" for "bliss." He could have selected a name related to Shiva, but "anandamide" rolls off the tongue nicely. A little later in 1995, Mechoulam's team discovered a second endogenous brain cannabinoid (2-AG) by processing rat brains and dog intestines. By then, Devane had returned to the United States to work in Julius Axelrod's laboratory at the National Institutes of Health. A team of these NIH scientists helped show more specifically how anandamide bound to the CB_1 receptor, which was first cloned in rats and then in humans in 1990. A cloned version of the human CB_2 receptor followed next in 1993. These were truly exciting times for cannabis scientists, with one discovery following another. Much of this nitty-gritty receptor work had been triggered in Axelrod's lab in 1990, when Lisa Matsuda found the DNA sequence that coded for CB_1 receptors. The next logical step was for a lab to breed genetically altered mice completely lacking CB_1 receptors and to see whether THC would still get them high. Unsurprisingly, it didn't. Because there was no specific "lock" in their brains for the THC to bind to, there were zero psychoactive effects from the drug. Instead, the lonely partial agonist molecule wandered around vainly seeking nonexisting cannabinoid receptors.

But all this novel molecular research raised much broader questions. What is the overall purpose and function of this molecular signaling network? Why are cannabinoid receptors present in the body? When did endogenous cannabinoids and cannabinoid receptors start appearing in animals? Next, let's tackle some of these big questions.

Why do we have an endocannabinoid system?

The human endocannabinoid system turns out to have a bewilderingly complex role in multiple key bodily and mental functions that at first glance seem unconnected. These physiological processes are as varied as helping guide normal brain development; regulating the output of other central-nervous-system neurotransmitter receptors; modulating pain, anxiety, mood, and response to rewards; regulating immune system function; and fine-tuning metabolism. What are the clues that helped us figure out the role of the ECS in these myriad processes? One memorable example: let's take a quick trip to Scotland to meet a remarkable woman whose peculiarities of perceiving pain trace back directly to her mutated ECS.

Silver-haired Jo Cameron lives next to the gloomy Loch Ness in Scotland. Ms. Cameron was born in 1948 with a unique combination of two genetic differences that render her (among other features) substantially insensitive to pain. For example, she can be ironing clothes and fail to notice that she has also inadvertently ironed her arm. She required absolutely no anesthetics or pain-

relieving medications when she gave birth to her children, or later in life when she underwent a major surgical procedure. What are these gene alterations? The first is a unique, small, previously unrecorded mutation in a recently identified gene located on chromosome 1, officially termed FAAH-OUT. (Presumably the gene was named by a geneticist with a sense of humor, plus memories of ’60s hippies.) FAAH-OUT is normally expressed in our brain and in large pain-processing nerve clusters located next to the spinal cord. Jo’s second difference is a common functional variant in the FAAH gene that reduces its effectiveness and activity. Together, these two distinct genetic hits significantly disable her body’s FAAH activity and subsequently her ability to experience pain from everyday scrapes, bumps, and bruises as well as major injuries. Jo’s blood tests reveal significantly higher-than-normal concentrations of anandamide (increased by 70%) and related cannabinoid compounds (some of which are triple normal levels) that are normally broken down by the FAAH enzyme. Because her MAGL enzyme is unaffected, Jo’s concentrations of 2-AG are entirely normal.

The result of Ms. Cameron’s combined genetic differences is that her endocannabinoid signaling is unleashed, and thus boosted, by her relatively ineffective FAAH. This newly recognized and likely unique two-hit condition has its upsides. As mentioned above, she experienced pain-free childbirth without an epidural. She barely batted an eye after being involved in two car accidents and can eat scorchingly hot chili peppers, which produce only a “pleasant glow.” But there are reciprocal downsides. For example, a severely degenerating hip joint that required replacement had generated no warning pain signals. And ironing your own arm is not recommended.

In addition, Ms. Cameron has other differences from the average person. One is her personality. She is unflappable and nearly always in a good mood: she scores 0 on standard anxiety-disorder and depression questionnaires. A second is her memory capacity. We will learn a little later in this chapter about anandamide’s function in the hippocampus, which is studded with CB_1 receptors like cloves in a potpourri. The hippocampus is essential in registering and laying down new memories, so it’s not surprising that Ms. Cameron also reports lifelong short-term memory problems. For example, she frequently forgets words in midsentence. The neurologists who tested her did not perform detailed memory testing to quantify this problem more precisely, so we don’t know whether she has deficits in particular types of memories. Although she frequently burns and cuts herself inadvertently because of a lack of warning pain signals, Jo has few scars, so perhaps her wound healing is speeded up.[8,9] Jo Cameron’s unique case is fascinating, not only because of the extraordinary way her condition has affected her life. From our perspective, it also clearly implicates the role of the ECS in pain control and in the regulation of both mood and memory.

How early did cannabinoid receptors originate in evolution?

Long before there was an endocannabinoid system, there were cannabinoid

receptors. The genes that code for CB_1 receptors (CNR1) are found across the animal kingdom in fish, frogs and other amphibians, birds, and mammals. Similarly, CB_2 receptor genes (known as CNR2) have been found in the spiky puffer fish from which we obtain the sometimes-deadly fugu sushi. Incredibly however, something that is essentially a mash-up between the CB_1 and CB_2 receptor genes exists in the primitive undersea invertebrate *Ciona intestinalis*. This beast (known technically as a sea squirt or vase tunicate) gets its intestinal name not from the fact that it inhabits somebody's gut but because its body's hollow, pillar-like form is reminiscent of an intestine. A colony of *Ciona* resembles a mass of guts anchored on an undersea rock. Up close, each pillar of *Ciona* is a few inches long and resembles a 5-year-old's attempt at making rigatoni, or a tiny condom with its end snipped off. For such a primitive beast, parts of its biology are surprisingly complex. The genome of this little creature is tiny—barely 5% of yours or mine, but almost every gene family in our human DNA is represented there. *Ciona* doesn't have a brain or even a proper nervous system. It does have axons, however, and so the available evidence suggests that cannabinoid receptors first evolved inside those primitive nerve cells to help regulate and coordinate them in performing one of the few activities in which sea squirts excel. Unsurprisingly, this is squirting. That behavior consists of sucking seawater into their bodies through a mouth siphon and spritzing it out the other end of its digestive tract.[10] The aptly named (in this context) US Department of Energy's Joint Genome Institute documents much of this technical cannabinoid genetic information on its website.[11]

At this point, the ECS trail gets even more bizarre. In addition to the unexpected occurrence of cannabinoid receptors in a primitive undersea creature, Italian scientists were also startled to find not only the presence of anandamide but also that of the major metabolic enzymes of the ECS, including NAPE-PLD and FAAH, inside the delicious and pricey black Périgord truffle, *Tuber melanosporum*.[12] These truffles do not express the endocannabinoid-binding receptors CB_1 or CB_2, or contain 2-AG (despite having all the RNA for producing DAGL and MAGL). So what on earth is the purpose of all of those cannabinoid components? Researchers concluded that anandamide and ECS metabolic enzymes must have evolved much earlier than endocannabinoid-binding receptors, and they speculated that anandamide might be an ancient attractant to truffle-eating creatures.

Putting the relevant dates together, we learned in the prior chapter that the cannabis plant emerged about 28 million years ago; truffles and their kin were around for about 128 million years prior to that, at the end of the Jurassic period, and sea squirts evolved about 550 million years ago. It appears that crucial nuts and bolts of the ECS are truly an ancient part of our biological history. Evolution continued to tinker with these archaic building blocks and ultimately produced the complex, multipurpose ECS.

How many cannabinoid receptors are there?

A few years ago, the answer to the question “How many cannabinoid receptors are there?” would have been “Two”: CB_1 and CB_2. That would have been followed by the elaboration that CB_1 is found in the brain, and CB_2 in the rest of the body. Now the answer would be “Four”: CB_1 and CB_2 plus TRPV1 and GPR55. That would be followed by the clarification that CB_2 receptors are also found in the brain.

So what about those two new cannabinoid receptors? Back to Jo Cameron. There’s a well-known video of Jo and her husband each chewing their way through a plate of ultra-hot chili peppers. Mr. Cameron quickly begins to turn red and sweat bullets, and, with his mouth on fire, he is unable to continue. Ms. Cameron continues to chew away unbothered, stating she experiences only a mild warm glow.[13]

That’s our introduction to TRPV1 receptors. In brief, any nasty stimulus, from a physically hot object to juice from a spicy hot pepper (such as a Scotch bonnet or scorpion), produces a characteristic hot, painful sensation. That’s why we describe hot peppers as “hot.” This sensory process occurs by activating so-called vanilloid receptors (known as TRPV1 sites) that are found mainly inside the pain-sensing neurons of the peripheral nervous system but are also located in the brain. TRPV1 receptors exist in part to warn us about heat-related pain. So why are they known as “vanilloid receptors”? Without examining their molecular structures, nobody would make the intuitive connection, but vanilla-bean flavoring and the key hot-pepper ingredient capsaicin are chemical relatives. Capsaicin (the molecule that makes chili peppers hot) binds highly specifically to TRPV1 receptors. So along with cannabis, tobacco, opium poppies, and cocaine, red hot chili peppers are yet another example of a plant whose natural chemicals alter body function by binding to specialized receptors. TRPV1 not only generates warning signals of heat pain, but it also modulates pain transmission more generally by boosting, lowering, or merging many types of pain information. These receptors also regulate body temperature, which explains both why they are found in the brain and why eating fiery peppers makes us sweat.

Here’s where cannabinoids enter the picture. It used to be thought that only heat or capsaicin could activate TRPV1 receptors. Surprisingly, the receptor sites are also molecular targets not only of anandamide but also of CBD.[14,15] This explains part of CBD’s role in modulating pain. Interestingly, chili peppers and anandamide synergize to reduce gut inflammation and reduce the severity of type 1 diabetes, in part through their joint action on TRPV1.[16] Perhaps in the future, patients with inflammatory bowel disease may shun Tums in favor of jalapeño-laced CBD edibles.

Cannabinoids also have an important involvement with yet another little-known entity known as the GPR55 receptor. This structure is a type of GPCR whose functions were long obscure, during which time it was classified as one member of a biological ragbag of so-called orphan receptors. This is another way of saying “This molecule is clearly a GPCR, but we have no idea what its function in the body might be.” Ultimately, researchers discovered that GPR55 was activated by

not only anandamide and 2-AG but also THC.[17] The receptor (like TRPV1) processes stimuli related to pain and inflammation, and it is distributed all over the brain, especially in the cerebellum. It has also been discovered in sensory integration sites next to the spinal cord, where information on pain and other sensations are blended and organized, and in the gut. Although GPR55 bears scant molecular resemblance to either CB_1 or CB_2 receptors, many scientists have suggested that because of its binding characteristics it should be recategorized as an additional member of the cannabinoid-receptor family and hence renamed the CB_3 receptor. This would be the molecular equivalent of finding a sibling that you never knew existed via a consumer genotyping outfit such as 23andMe. This reclassification is not yet scientifically official however. What we can infer though is that GPR55 is yet another mechanism through which the ECS controls pain signals in the nervous system.

What are some broad properties of ECS components?

Let's begin with endogenous cannabinoids. When they bind to their respective CB receptors, both anandamide and 2-AG are agonists. That is, they switch on (activate) the receptor to produce a cellular response. While brain anandamide generally has a diffuse modulating effect on multiple neurons, it also has highly specific effects in particular brain regions. This illustrates another example of the ECS being more complicated than we first imagined. Some researchers summarize one of the ECS's primary purposes as homeostasis—in other words, maintaining key systems in the body on an even keel.[18] Meanwhile, 2-AG is more straightforward in its activity, backtracking within the synapse from a post-synaptic nerve cell to influence pre-synaptic neurons (which is why it is sometimes termed a "retrograde messenger"). Unlike anandamide, it has a more precise point-to-point profile of action. It's easy to see how such activity might act as a local feedback mechanism from post- to pre-synaptic neurons.

As well as their primary effects in the ECS, both anandamide and 2-AG have secondary actions on other key neurotransmitter systems, including circuits ruled by glutamate and dopamine. This activity outside the ECS enables endocannabinoids to balance the overall stirring up versus calming down of neural inputs across the entire nervous system, in both the short- and long-term. In a tit-for-tat system of regulation, release of those other neurotransmitters in turn can trigger neurons to squirt endocannabinoids that then act on pre-synaptic CB receptors to regulate neurotransmission. You can think of this round-robin of activity as a kind of self-regulating feedback loop, again consistent with the hypothesis that the ECS may have a role in homeostasis.

Thus from one perspective, there are straightforward tissue-specific effects of endocannabinoids; this compound on that receptor in this organ elicits this precise effect. But from another more general perspective, the body's cannabinoids also act as nonspecific cross-system modulators. They tweak numerous and diverse molecular processes, including immune function, pain perception, appetite,

metabolism, cognition, and motor coordination. From this point of view, endocannabinoid molecules are acting more like a team of busy office managers, ringmasters, or orchestra conductors. Moreover, cannabinoids initiate multiple downstream molecular signaling mechanisms inside cells, resulting in altered cell functions. Here they act more like online influencers.

How did people figure out what the ECS and its components do?

Over the years, scientists have gradually chipped away at the varied complex functions of the ECS in order to understand better how each works. To do so, they have used many different strategies. One approach is learning from experiments of nature, like Jo Cameron. Others include employing genetic tools to create experimental animals completely lacking CB_1 or CB_2 receptors, or having reduced receptor numbers, in order to study the resulting modified animals' behavior and biology. With such genetically modified beasts, researchers are able to determine the effects of those cannabinoid molecules that are not mediated by cannabinoid receptors. More explicitly, if they dose a CB-receptor-deficient animal with a cannabinoid such as THC and something important changes in its behavior or physiology, they can conclude that effect could not have been driven by CB receptors, as this creature had none. Other research has focused on pharmacological engineering to alter the shape and function of cannabinoid receptors by tinkering with the genes coding for them. Additional strategies have employed synthetic cannabinoid molecules similar to anandamide or THC but designed in pharmacology laboratories to bind hundreds of thousands of times more strongly to CB receptors. Predictably, some of these designer drugs have escaped the research lab to resurface as synthetic cannabinoids such as "Spice" and "K2."

More recently, researchers have discovered drugs that influence (for example, block or rev up) the effects of the enzymes that synthesize or break down endocannabinoids, such as FAAH. They've then used these novel pharmaceuticals to build up or deplete the ligands involved to much higher or lower levels than normal. This allows scientists to study the effects on health and behavior of the modified lab animals. These ongoing experiments have clarified that the ECS is a unique, complicated, vast-ranging cell-signaling system whose functions are only beginning to be unraveled. So let's take a closer look at some of that research.

Molecular studies of receptor structures

What do CB_1 and CB_2 receptors look like? In layperson's terms, these GPCRs are present on cell surfaces as tiny, precise, perfectly designed pieces of machinery that resemble a mash-up of a nanobot and a series of Thomas Joynes vortex sculptures tossed together with a handful of Slinky springs. If you want more help in visualizing a CB receptor protein in 3D, you can borrow this idea from the Richard Powers novel *The Gold Bug Variations* and turn it into your very own science project.[19] First, take the cardboard tube from a roll of kitchen towels and

separate its seam so that it becomes a loose cardboard spiral. Repeat this process six times so that you have seven partly unwound cardboard rolls, representing the seven transmembrane domains of the CB receptor. Then spray-paint one of the rolls yellow, one red, two green, one orange, one teal, and one navy blue. Stack them in a vertical row from left to right, rearranging them slightly so that the greens cross behind the red and the teal hides unsuccessfully between the red and blue. Then bend the bottom of the red so that it crosses all the way over to the right side. Now you are the envy of your friends, with your very own three-dimensional artist's model of a CB_1 receptor.

Alexandros Makriyannis, a pharmaceutical chemist and acknowledged expert in the field of cannabinoid compounds, formerly directed a research lab at the University of Connecticut in the early 2000s. At that time, he would attend lectures at my home institution, and we'd chat about his latest cannabinoid discoveries. Several years ago, he moved his lab to Northeastern University in Boston, where over the last few years he has helped decipher the active crystal structure of CB_1 and CB_2 receptors. His work is the type of complicated, finicky, and precise science that requires a large-scale team effort. Indeed, Alex has been part of several international collaborations, teaming up with research scientists from Moscow, ShanghaiTech University, and Beijing, as well as other US universities. In a series of fascinating publications, these investigators have helped unravel the structural intricacies of the cannabinoid receptors, how to build them inside bacteria, how their 3D shapes are altered when occupied by agonists and antagonists, and where novel molecules can bind in various nooks and crannies on the receptors to alter their properties. In addition, they have genetically engineered mutations in the receptors and altered their protein recipe to make it easier to study without altering its structure or function.[20–23] Theoretically, one could use THC to probe some of these questions on CB_1 receptors. But because it's a partial agonist, it's potentially too wimpy to fulfill that purpose. What are really needed to figure out how these receptors work are specially engineered extra-powerful "super-agonist" and antagonist molecules that fit precisely and decisively into the molecular binding pockets in the receptor. Using such techniques, cannabinoid receptors reveal surprising complexity. For example, when bound by these specially designed cannabinoid ligands, the CB_1 receptor morphs its 3D shape like a Transformer. The molecular binding pocket, where these ligands dock, can change its volume by more than 50% to accommodate active molecules of various sizes, shapes, and functions. Unlike our simple cardboard mock-up, on the surface of all of these twisted, pretzeled-together Slinky protein structures are additional niches and crevices separate from the originally discovered binding pocket. Into these molecular niches a variety of novel cannabinoid compounds can insinuate themselves and alter the properties of the receptors. And because the cannabinoid receptors act as fancy molecular toggle switches, the different resulting 3D shapes will pass along different molecular messages with new downstream effects on cellular targets. These "unofficial" binding sites hidden within the cannabinoid receptor turn out to be very different functionally depending on whether they

belong to CB_1 or CB_2 receptors, despite the latter's superficial resemblance and 40% structural overlap. Consequently, substances that activate one receptor can actually weaken or inhibit signaling on the other, in what has been described as a "yin and yang" relationship between CB_1 and CB_2.[24] All of this complicated work has practical consequences in helping us understand basic principles of rational endocannabinoid drug design.

How do THC, CBD, and other plant cannabinoids interact with the endocannabinoid system?

We just reviewed the behavior of endogenous cannabinoids at their receptors. The obvious next question is how plant cannabinoids behave at the same specialized receptor sites. Let's begin with THC, which is a lipid and partial agonist at the CB_1 receptor that binds to this docking site and switches it on, albeit rather weakly. Although its binding to the receptors is less specific than that of endogenous cannabinoids, it hangs around for much longer at the synapse. Its effects last for hours rather than microseconds. THC effects persist because the molecule is not broken down by enzymes such as FAAH or MAGL but metabolized slowly in the liver. In addition, as a lipid, THC and some of its metabolites are stored in the body's fat cells for days to weeks. The bottom line is that THC's partial agonist effects are much more persistent than those of natural endocannabinoids such as 2-AG, even though those are full agonists. In addition to its actions at CB_1, THC is a weak CB_2 agonist and activates GPR55 and TRPV2 receptors, as well as yet other receptor types.[25] When THC is given to lab monkeys, they literally chill out and drop their body temperature by a degree or two, likely due to interactions with brain TRPV1 sites. Similarly, when THC is given to rats, they develop the rodent equivalent of couch lock, or at least significantly drop their spontaneous activity.[26] Rats also become more pain-tolerant after being dosed with THC, as we might expect from cannabinoid interactions with both opioid and TRPV1 systems. Preliminary human clinical trials suggest that THC might be an effective pain reliever,[27] although this is controversial.

Let's move on to CBD, a compound whose mode of action is both less understood and much more complex than that of THC. Despite barely binding to cannabinoid receptors, CBD is a weak low-affinity, noncompetitive CB_1 receptor negative allosteric modulator.[18,28,29] CBD may also act as a weak agonist at CB_2 and TRPV1 sites. Outside of the ECS, it is an agonist at serotonin $5\text{-}HT_{1A}$ receptors and a positive allosteric modulator of mu opioid receptors.[30] Cannabidiol's action at CB_1 receptors may reduce the ability of CB_1 agonists such as THC to bind there, providing a simple explanation of how CBD modulates THC activity. Recalling the earlier discussion of the many sub-pockets and secondary binding sites within the CB_1 receptor complex, CBD does not bind to the primary site at which THC and anandamide dock. Instead, it snuggles up to another part of the CB_1 protein called the "allosteric binding site" (ABS). When

CBD gloms onto the ABS, the entire CB_1 receptor subtly changes shape. In this case, that shape-shift makes it harder for CB_1 agonists such as THC to bind there, temporarily blunting their effect. Basically, CBD is a molecular dimmer switch at CB_1 receptors.[31,32]

Despite its efficacy, the drug's underlying pharmacological mechanisms of action in treating epilepsy and psychosis are yet unknown. There is no shortage of hypotheses regarding receptor systems outside the traditional endocannabinoid universe via which CBD exerts these effects. Scientists have speculated that the drug may be an antagonist of the orphan receptor GPR55,[33,34] an allosteric modulator of the mu and delta opioid receptors,[30] or a modulator of electrical currents within the TRPV1 receptor. Any of these ideas is plausible, but none is proven.

It's sometimes easy to forget that the cannabis plant contains scads of other cannabinoid compounds. Most of these are unexplored, both in terms of potential therapeutic possibilities and their biological activity in the ECS and other systems. To pick one example, preliminary work shows that delta-9 tetrahydrocannabivarin (THCV), another naturally occurring cannabinoid in the marijuana plant, modulates the effects of THC via direct blockade of cannabinoid CB_1 receptors. In that respect, it behaves like a first-generation CB_1 receptor inverse agonist, such as rimonabant, the abandoned ECS-acting appetite-suppressant drug. In test tubes, THCV is also a potent high-affinity CB_1 receptor antagonist. But when given to live animals, it mysteriously has very few if any of the behavioral effects typical of CB_1 receptor antagonism. THCV also has high affinity for CB_2 receptors and acts there as a partial agonist, differing in that respect from both CBD and rimonabant.[28] Cannabigerol, another plant cannabinoid, acts as a weak CB_2 antagonist.

The point of discussing this complexity is to illustrate that of the over one hundred cannabinoids synthesized by the cannabis plant, the handful that biochemists and neuroscientists have examined thus far exert a dizzying complexity of effects inside and outside of the ECS. Many of these compounds have completely opposite modes of action, so that how the body reacts to them in combination is pretty much unknown. The same holds true for their medicinal and subjective effects. THC and CBD are the celebrity compounds but only around 2% of the cannabis plant's total cannabinoid census. Just as we would never think to draw conclusions regarding the beliefs, opinions, and customs of people in the entire United States by interviewing individuals only in New York and LA, these numerous non-CBD or non-THC cannabinoid compounds require independent and careful study.

CBD interactions with THC

An up-to-date review of this important topic can be found in a recent publication. Briefly, the popular belief is that CBD initiates brain changes that are opposite to those resulting from THC, thus in some sense protecting the brain from the

harmful effects of THC on, for example, cognitive performance and psychosis-proneness. This interrelationship is much more complex than was initially portrayed, however, as I'll explain. Thinking of CBD as some type of "anti-THC" is overly simplistic. For one thing, CBD may change THC levels in the blood before the latter even gets to the brain by altering THC's distribution in the body as well as its breakdown to simpler chemicals and subsequent excretion.[26] In addition, the order of drug administration may be important. CBD given prior to THC has different effects than when the two compounds are given at exactly the same time. Third, the ratio of the two compounds may make a big difference. Finally, the range of CBD and THC doses that have been explored in human studies is considerably more limited than the range that has been administered to lab animals. Another part of what makes the THC-CBD interrelationship even more complicated is that, beyond a simple tug-of-war, the two compounds have complicated and separate effects of their own that blend and combine unpredictably when they are administered together. Sometimes the two drugs' effects on a particular function are in the same direction in one study and opposite in another. For example, both compounds are effective in reducing pain but probably through different mechanisms. THC effects on pain in mice and rats are amplified by CBD, so here the two effects apparently are additive. But that is the exception to the rule, and even in this case the picture is likely more complicated.

The ratios of THC and CBD in marijuana flower are relatively constrained and move in opposite directions. This means when cannabis contains more THC, the CBD content will fall correspondingly. Vaporizer cartridges, however, now allow people to self-administer a wide range of ratios of the two compounds (for example, equal ratios of each cannabinoid, which don't occur in nature). Dose seems to matter a lot. Different CBD and THC doses may have varying effects, in a so-called biphasic pattern. In some experiments, low doses of CBD reduce anxiety but higher doses don't. This further complicates the well-known fact that low doses of THC reduce anxiety, but higher doses tend to make people increasingly anxious. In other experiments, neither low nor high doses of CBD were effective in reducing the anxiety associated with public speaking, but medium doses were. Nobody has yet explored in detail the question of how different doses of CBD modulate those of different doses of THC in humans to produce particular psychological effects such as anxiety or paranoia.

Along these lines, research using relatively limited dose combinations has shown that CBD can modulate particular THC-related effects in humans. For example, in one experiment, pretreatment with oral CBD reduced cognitive impairment and paranoia produced by subsequent intravenous THC administration. CBD at particular doses also protects against THC's tendency to raise anxiety.[35–37] When administered to cannabis users at 200 mg a day for 10 weeks, CBD improved cognitive and psychological status and (on MRI scans) increased volumes of the hippocampus, part of the brain crucial in memory.[38] On the other hand, THC impairs working memory in rhesus monkeys. When CBD was given alongside the THC doses, it not only failed to help the memory

problems but may have worsened them,[39] although it did reduce other cognitive problems caused by THC. Nothing is straightforward, and CBD is clearly not a simple antidote to THC's undesirable effects. Acute exposure to THC in humans and animals also causes short-lived impairments in short-term memory, decision-making, and abstraction.[26] CBD acutely administered by itself does not seem to be associated with cognitive problems and may partially dilute those provoked by THC, at least when the two are administered orally.[40] In conclusion, the relatively small amount of human research to date suggests that CBD may offer some protection against some acute learning deficits provoked by THC at certain doses and under particular circumstances. Unraveling what's going on here is ultimately important not only for teens using cannabis but for users of medical marijuana in such conditions as multiple sclerosis, where cannabis may improve muscle spasms and pain but at the potential cost of worsening any underlying cognitive deficits. If a dab of the right amount of CBD can offset the cognitive side effects, we need to know that. And the route to understanding such issues will begin with a more complete understanding of exactly how CBD exerts its effects.

What are synthetic cannabinoids?

A little earlier we discussed how specialized cannabinoid molecules designed in the lab are used as molecular tools to figure out the structure and function of cannabinoid receptors. Such synthetically designed cannabinoids, for example the active agents in "Spice" and "K2" are CB_1 super-agonists. As such, they bind super-tightly and enduringly to this cannabinoid receptor subtype. Once these designer drugs have latched onto the cannabinoid receptors, they keep them switched on for hours or even days, rather than the milliseconds of activation normally produced by the body's own cannabinoid agonists such as anandamide. To use the light-switch metaphor I employed earlier, these synthetic drugs not only switch on the light and keep it on, but they replace the bulbs with those you'd ordinarily find in football-stadium floodlights.

In the 1970s, the Pfizer drug company designed the experimental compound named CP55940. This mighty molecule possessed super-agonist effects. Further synthetic cannabinoids were synthesized in the 1980s as lab tools to help scientists study the cannabinoid system by binding tightly to its receptors. Most such first-generation synthetic cannabinoids bear prefixes to designate the chemist who first designed or synthesized them, or the company of origin. For example, "AM" compounds such as AM-2201 were designed by the cannabinoid researcher Alexandros Makriyannis, whom we met a few pages ago. Similarly, "JWH" compounds are named after perhaps the most well-known synthetic cannabinoid chemist, Clemson University's John W. Huffman. In the 1990s, Huffman designed and produced hundreds of designer cannabinoid compounds for research and medicinal purposes. Little did he suspect that many of his super-agonist compounds would later be repurposed illicitly as toxic street drugs. Instead, he had crafted them as molecular probes of cannabinoid receptors, precision tools to

unravel the ECS. Perhaps inevitably, home-brew chemists seized on Huffman's original scientific publications as recipe books and found in them the means of making a quick buck by synthesizing and dealing these compounds. In theory they should produce an extended super-high with the advantage of not showing up on regular urine screens for THC. The resulting products were first reported as being sold illicitly in the United States in November 2008. Currently these synthetic cannabinoid drugs are mainly synthesized in and imported from China in liquid form. The chemical is sprayed onto cheap neutral dried herbs in the United States and sold relatively inexpensively in rest stops and gas-station convenience stores as "air freshener" and "potpourri" (which fools nobody) branded as "Spice," "K2," and similar products. Most such packets bear the disingenuous disclaimer "not for human consumption" as a kind of legal liability CYA. Synthetic cannabinoids are also sold in e-cigarette cartridges as "c-liquid" under brand names including Kronic. Their effects on hapless consumers are unpredictable and potentially dangerous. The products are often contaminated with unknown chemicals, and their health consequences can be dire. After hitting the market, emergency calls to poison-control centers related to these compounds began to skyrocket. In 2019 in New Haven, for example, there were numerous hospitalizations resulting from their use. First responders attended to more than 50 very sick people in a matter of several hours in the central New Haven Green area alone. Consumer behavior being what it is, the next day several of the same individuals were back in the same emergency department, either not having learned their lesson the first time around or being unwilling to abandon a product they had paid good money for.

Illicit synthetic cannabinoids used recreationally bind not only as predicted to CB_1 receptors but, depending on their composition and the sloppy lab processes used to create them, often have other unwanted effects on other metabolic systems in the body. Among other varieties of medical mischief, they can produce states of prolonged delirium, psychosis, huge spikes in blood pressure, dangerous increases in heart rate, seizures, coma, and in some cases even death.

There is a cat-and-mouse game with regard to synthesizing and selling these substances. Beginning in 2011, some of the original compounds were banned by the DEA, including a handful of Huffman's progeny. But as soon as a particular synthetic cannabinoid is analyzed, identified in government labs, and declared illegal, the manufacturer rapidly changes the recipe to produce a related still-legal chemical structure. This temporarily avoids its detection and identification as an illicit substance, until the novel compound too is ID'd and reclassified as illegal—at which point the rogue chemists merely switch to the next synthetic cannabinoid, and so on. Many of these compounds are fairly quick and easy to synthesize, so that the bait-and-switch or whack-a-mole cycle is a rapid one. Thus, unwary users can never be certain what they have purchased. Huffman, still alive and productive as of this writing, labels synthetic cannabinoid users as "idiots" for putting substances never properly tested in humans into their bodies and brain receptors.[41] So far, over 150 of these ultrapotent compounds have been identified.

Synthetic liquid cannabinoids known as "mojo" first appeared in US prisons in

2010. They proved irresistible to some inmates because the substances were powerful and took up much less space than traditional cannabis, thus being easy to conceal. Moreover, they had no odor and were not detected by drug-sniffing dogs. Urine toxicology screens designed to pick up THC came up negative, so that routine testing failed to detect use. In addition, the compounds were hard to identify through analysis because of continual cycling into new synthetic formulas. To the terminally bored, long-term incarcerated individuals, these designer cannabinoids were like catnip. Some mojo-using prisoners "started having seizures and aneurysms and some people were freaking out and getting paranoid and scared. . . . They were going crazy on it. But they loved it." [42] Such synthetic cannabinoids are so toxic for several reasons. Compared to cannabis and THC, they have hugely greater affinity for CB_1 receptors and greater activity at the receptors since they are full-on versus partial agonists (such as THC). They are much longer lasting in their biological activity there through their own effects and those of their metabolites. Also, they lack possible offsetting effects of CBD. In addition to ECS activity, these synthetics have multiple unpredictable targets outside the CB_1 system. In my opinion, the sale of these drugs would likely dwindle significantly if recreational marijuana were legal and affordable.

What else in the cannabis plant acts on the ECS?

Chemical wizardry is not restricted to cannabinoids but also extends to terpenes, compounds manufactured in the cannabis plant, which we will encounter in Chapter 8. The terpene beta-caryophyllene, found in not only cannabis but also other plants (such as black pepper), is a CB_2 agonist. By tinkering with this substance, chemists created an FAAH-specific COX-2 inhibitor drug that resembles nonsteroidal anti-inflammatory compounds like ibuprofen or naproxen but lacks any of the typical GI side effects of drugs in this class (indigestion, ulcers, GI bleeds). Surprisingly, some of these non-cannabinoid drugs have significant effects on the ECS. For example, the over-the-counter painkiller acetaminophen (marketed as Tylenol, among other brands) has metabolites that indirectly activate CB_1 receptors and modulate TRPV1 sites.[4]

We've discussed how chemists can brew cannabinoid receptor agonists from scratch in the lab. But what would happen if people began the recipe with chemicals derived from actual cannabis plants? This what-if question is now a reality. As a result of the 2018 Farm Bill that legalized the regulated production of hemp (cannabis plants containing less than 0.3% of THC), pharmaceutical chemists have been able to operate in a kind of legal "gray zone." They can extract legal CBD from hemp but then alter it chemically to make cannabinoid compounds not found naturally in the cannabis plant. The desired end result is novel cannabinoids, some of which possess intoxicating (and salable) properties but are not yet designated as illegal. One example is the now-notorious delta-8 tetrahydrocannabinol, a close chemical relative of THC (delta-9 tetrahydrocannabinol), that is sold as an intoxicant throughout the US. Because of

its derivation from hemp, delta-8 is not clearly illicit. Legislators, however, are scrambling to outlaw this compound and other similar hemp-derived intoxicants such as THC-O-acetate. This process has proven a struggle because of the ambiguous wording of the Farm Bill and its exclusive focus on controlling THC. Although distinct from naturally grown cannabinoids that have not been chemically altered, such molecules as delta-8 are not truly synthetic (meaning, they're not made from scratch using pure chemicals in the lab). For that reason, they are often referred to as "derived" or "semi-synthesized" psychoactive cannabis products. Consumer reviews are mixed. Many users claim that delta-8 produces a qualitatively different and inferior high compared to classic delta-9 THC.

Measuring human CB_1 receptors with PET scans

How can we count the number of cannabinoid receptors in the living human brain? Accomplishing that allows scientists to answer such questions as "What happens to these receptors in people who smoke cannabis regularly?" The inverse agonist drug compound MK-9470 binds strongly to CB_1 receptors in the human brain—so strongly in fact that tiny doses can be given in a radioactively labeled form sufficient to safely produce an accurate map of receptors in the brain and enable us to count their numbers. This technique is called "positron emission tomography," also known as a PET scan. The fact that minuscule doses of MK-9470 are sufficient means that there are no undesirable drug effects associated with the studies. Thus, the dose of administered radioactivity can be very small. And the radioactive compound decays quickly, so exposure is low. Through this and similar approaches, we can identify where the highest concentrations of CB_1 receptors are located in our brains, whether they are changed in stoners compared to non-users (the numbers fall significantly), and what such measurements reveal in the brains of people with conditions such as schizophrenia.

What body functions is the ECS responsible for?

We learned a little bit about the body functions the ECS is responsible for from the case of Jo Cameron. More comprehensive reviews can be found in a series of recent articles.[1,3,4,43,44] A list of the activities the ECS participates in is seemingly exhaustive and wide-ranging over almost every known body system. As well as neural signaling, it plays an important role in blood-pressure regulation, immunity, inflammation, sleep, memory, gut motility, fat metabolism, insulin sensitivity, bone development, pain control, and fertility. The cannabinoid system is with us from our very first moments. The early developing embryo is covered in cannabinoid receptors that help it implant in the wall of its mother's womb.

The ECS, although biologically ancient, is so recently discovered and novel that much about it remains to be uncovered and understood. It is also a hot area for pharmaceutical companies to investigate. Cannabinoid receptors and endocannabinoids are widely disseminated through multiple body systems,

suggesting they play an important role in many physiological processes and as promising targets for novel drugs. Some of these prospects are already starting to pay off. For example, some cannabinoid drugs delay tumor progression,[45] while others help treat kidney fibrosis.[46] Many of these compounds, however, have yet to make it into routine clinical practice. One factor that makes studying the ECS so complex is that, at least at a brain level, many of the effects of cannabis and of THC are biphasic. That is, a low dose may have one effect (such as anxiety reduction), whereas a higher dose has exactly the opposite outcome.[47] Consequently, nothing about the ECS can be taken for granted, and every feature requires careful exploration by both consumers and scientists.

Thus, we need to think beyond the cannabis plant more broadly, in terms of how to manipulate the ECS for therapeutic purposes (something we will review in more detail in Chapter 9). In addition (as discussed above), we need to further understand the intricacies of molecular structure of cannabinoid receptors in order to custom-design novel drugs that interact with them in predictable ways. But first, let's try and take one argument off the table. A common assertion raised by individuals opposed to medical cannabis is that one drug could not plausibly be effective (as has been suggested for cannabis) in treating, among other disorders, arthritis, depression, glaucoma, chronic pain, anorexia, epilepsy, dementia, Parkinson's disease, dystonia in multiple sclerosis, anorexia in AIDS and cancer, and inflammatory bowel disease. But to recap what we've just learned, because of its seemingly ubiquitous distribution, it is at least feasible that drugs acting on the endocannabinoid system really could have far-flung and multiple beneficial (or deleterious) effects on the brain and body through a variety of different mechanisms. With that mental math in mind, let's dig a little further into some of what's been discovered about the normal role of the ECS and how it interacts with the molecules in the cannabis plant.

Brain development, brain maintenance, and beyond

Clues to what the ECS does can be garnered from its distribution in the body. Though its reach may be far and wide, nevertheless it is especially concentrated in some areas and cell types. For example, large numbers of CB_1 receptors are present in impressive quantities in particular parts of the brain. I list a few here, followed by an overly simplified summary of some of the processes they are likely involved in (in parentheses). Their highest density is in the prefrontal cortex (various cognitive functions), hippocampus (memory), cerebellum (balance, cognition), cingulate gyrus (choice and decision-making), and basal ganglia (cognition, reward, motor coordination). More modest quantities exist in the basal forebrain (sleep). Anandamide injection into rats' basal forebrain produces increases in slow-wave and REM sleep. CB_1 receptors also abound in the amygdala (emotional regulation and fear processing), nucleus accumbens (reward), peri-aqueductal gray (pain processing), and hypothalamus (appetite). Notably there are few or no CB receptors in the brain stem or primary motor

region. The former probably accounts for why cannabis even at high doses has almost no short-term paralyzing effects on breathing or cardiac function, unlike alcohol and opioids. Or as my stoner friends like to remind me, the toxicity is sufficiently low that even though ingesting huge amounts of THC might make you feel remarkably unpleasant, it won't kill you. As they put it, "Cannabis overdose deaths now equal the number of people killed by unicorns," and "Cannabis is not illegal because it's dangerous: it's dangerous because it's illegal."

In addition to the functions described above, cannabinoids play a vital role in sculpting our developing brains. The ECS is crucial to normal fetal brain growth and continues to play an important part in regulating multiple aspects of normal brain development and maintenance through adult life. Anandamide, for example, functions in early brain development to influence the formation of new synapses, fosters the growth of just-born neurons, and helps guide these developing fetal nerve cells to their correct targets in the busily expanding brain. In addition to anandamide, 2-AG plays an important role in the growth and guidance of neurons. Both cannabinoids also help axons to grow, provoke new neurons to develop and mature, and beyond individual cells, aid in the development of more complex neural circuits. These important brain-sculpting and guidance functions continue through infancy, adolescence, and early adulthood. CB_1 receptors in particular are also required for the growth of axons.[48] Later, in adolescence, anandamide contributes to pruning or paring down existing synapses to help brain connections become fewer in number but more efficient in function.[49] Some researchers have argued that these persisting ECS activities in the brain may be one reason that activating the CB_1 receptor with THC in a way that exceeds normal physiological levels can produce ill effects on the developing brain when cannabis is used in adolescence. Increased risk for schizophrenia may be one consequence.

What other behaviors significantly involve the ECS?

The distribution of CB_1 receptors in the brain allows us to infer some of their physiologic effects. Scientists thought initially that CB_2 receptors were present only outside the brain and restricted to the immune system. Both these assumptions turned out to be wrong. It is now known that CB_2 receptors have an extremely wide distribution in multiple body systems, including the brain.[50] First, let's examine what's known about CB_1 function in the brain. There is a moderate concentration of these receptors in the nucleus accumbens, one node in an important circuit containing high concentrations of dopamine (DA) neurons and their receptors. This portion of the DA system imbues incentive motivational value into stimuli that we encounter in the world. That's a fancy way of saying that one vital function of brain networks that use this neurotransmitter is to prioritize what's truly important in the environment and needs attending to, and that DA plays a key role in these value judgments and subsequent behavior. The ECS modulates and influences this dopamine-driven monitoring and judging process, a topic nicely reviewed in several articles.[51,52] More generally, in addition to these

influences on reward and motivation, the ECS has additional important and broad interactions with the DA system that influence alertness and possibly risk for addiction and schizophrenia.

In short, the ECS interacts with the dopamine reward system on multiple levels via CB_1 receptors. Brain endocannabinoids appear to dial up or down the positive reinforcing effects both of natural rewards and of abused substances. This ECS tweaking of reinforcement and reward occurs through endogenous cannabinoids interacting not only with DA but to a lesser degree with parts of the opioid neurotransmitter systems. Using plant cannabinoids temporarily retunes the reward system.

Acute stimulation of CB_1 receptors in rats and mice leads indirectly (via other neurotransmitters such as glutamate) to DA release in reward regions, similar to other recreational drugs such as cocaine. But compared to other addictive substances, this effect is rather unimpressive.[43] Laboratory animals show complex and unpredictable behavioral responses to CB_1 agonists such as THC, often very different from what we observe in humans. In monkeys and rats, these agonist compounds can reinforce behaviors under some conditions or doses but not others. They can be rewarding in particular circumstances or anxiety-provoking or unpleasant in others.[4]

Seemingly every behavioral science teacher shows students grainy videos of rats pressing a lever to deliver electrical stimulation to brain reward regions, something they (the rats not the students) will perform to the point of exhaustion. Similarly, rats can be trained to lever-press to deliver micro doses of potentially abusable substances to appropriate brain reward locations. The late Joseph Brady at Johns Hopkins and his fellow researchers produced hundreds of papers examining just how hard various animals would work for particular drugs. These behaviors generated accurate models predicting a particular drug's abuse potential in humans. In the case of rodents given access to cocaine and opioids for example, it's easy to elicit lots of repeated lever pressing, showing that rats find these substances rewarding and presumably pleasurable. For THC, the equivalent effects are mixed and not very impressive. Rats are reluctant to self-administer THC, although squirrel monkeys are a little more enthusiastic. Injecting small amounts of anandamide or THC directly in small amounts into brain reward areas in animals elicits no classic "drug of abuse profile." This lack of effect is completely different from what is seen with other abused recreational drugs. In fact, some cannabinoid-like medications actually reduce dependence effects of other drugs of abuse including nicotine, alcohol, opioids, and cocaine, at least in lab animals.

With enough effort and ingenuity, researchers can coax lab rats and monkeys to self-administer cannabinoid agonists, but as mentioned above it's difficult to get them to do so. This finding seems counterintuitive, since cannabis dependency is well established in humans, and our natural assumption is that laboratory animals would enjoy getting high too. The fact that they usually don't is one reminder of important behavioral and brain differences between people and animal models. Rewarding effects of cannabinoids in lab animals are also very dose sensitive. The

injection of larger doses of CB_1 agonists is quite negatively reinforcing.[51] The bottom line though is that while the ECS modulates reward-related behaviors, it does so in quite complex ways.

So far we've confined our discussion to brain CB_1 receptor sites. What's the function of brain CB_2 receptors? They seem to be localized on specialized non-neuron brain cells known as "microglia," as well as on midbrain dopamine-reward neurons. Preliminary experiments suggest that activating these DA-reward-neuron-related CB_2 sites changes behavioral responses to both cocaine and alcohol, at least in mice. CB_2 receptors in animal brains are involved in anxiety reduction and in modifying the animals' response to stress. Their precise role in the human brain remains to be worked out. As a reminder, both the cannabinoid receptors GPR55 and TRPV1 are also located in various brain regions.

As well as complex activities in the dopamine signaling network, the ECS also has effects on opioid receptors that are an integral component in our ability to tolerate pain. So let's discuss the role of cannabis as a pain treatment. Briefly, cannabinoid receptor agonists are associated with pain relief in animal models of both chronic and acute pain. Part of this effect occurs through the opioid system. Indeed, the specific type of opioid receptors in the brain and spinal cord to which pain-relieving opioid drugs such as morphine, heroin, and OxyContin bind are often located right next to CB_1 receptors, suggesting that the two influence one another (what scientists term "cross-modulation"). Under some circumstances, opioid and cannabinoid receptors will actually link up functionally, in a kind of temporary hookup, to alter each other's biological properties. Thus, there is at least some evidence that cannabis's effect on pain reduction is not just due to release of opioids but involves these sorts of complicated cross-receptor interactions. In addition, peripheral CB_2 receptors may modulate pain outside the central nervous system, not only through inhibiting inflammatory responses but surprisingly by causing release of endogenous opioid peptides. Cannabis-derived agonists such as THC likely relieve pain by encouraging the body to synthesize or release endogenous opioid chemicals such as endorphins in the brain and spinal cord. Recent studies from the University of New Mexico show that substantial pain relief was reported by patients who used high-THC cannabis flower across a variety of medical conditions.[27] Relatedly, individuals who use medical or recreational marijuana and then need to undergo major surgery rate their post-surgical pain as significantly more severe than non-users.[53] A similar phenomenon occurs with individuals who are taking preoperative prescribed opioid pain medications and have them discontinued in the hospital prior to surgery. In both cases, an effective pain-relieving medication is stopped as part of routine care, and due to tolerance to the drug, the body's pain sensitivity rebounds. Thus, a number of threads of evidence suggest that cannabis may be a potentially effective pain reliever, as might be intuited from the case of Ms. Cameron in Scotland.

Understanding these interactions between cannabinoids and the opioid system may seem abstruse, but if we want to figure out whether medical cannabis might help reduce opioid consumption in individuals battling chronic pain, dissecting the

underlying neuroscience might help to guide clinical practice. Compared to opioids, cannabis has a significantly more benign side-effect profile and is less physically addictive. Thus, a harm-reduction argument is often made for cannabis's role as an opioid substitute in managing severe chronic pain, a claim that we will examine in more detail in Chapter 9. ECS and opioid interactions turn out to be only part of why cannabis has been known for millennia as an effective pain reliever. Right now though, we lack the appropriate double-blind, placebo-controlled trials with sufficient patient numbers to draw any firm conclusions regarding how safe and effective cannabis is in relieving acute or chronic pain.

The question of how chronic cannabis use might trigger later psychosis has focused to a large extent on THC provoking possible alterations in the DA system. One obvious key experiment to test that hypothesis is to let volunteers smoke cannabis or to inject them with intravenous THC. Then one can use brain-imaging techniques such as PET scans that employ short-lived mildly radioactive isotopes to probe DA receptors. PET scans would enable us to see whether cannabis actually triggers DA release compared to placebo. Several labs have tried exactly this approach to address the cannabis-DA question. Here, humans differ from rats. In rodents, administering THC and related compounds indisputably causes significant brain dopamine release. The results in human volunteers are more confusing and contradictory, and until recently the evidence wasn't very convincing that acute exposure to THC caused significant brain dopamine release. Ansel Hillmer, a Yale University scientist, developed a novel paradigm that used a PET camera to capture short-lived dopamine release in response to smoking cannabis.[54] As a result, the answer to a simple, obvious hypothesis (cannabis causes excessive DA release, which leads to psychosis) seems to be a little clearer. There is also some evidence of a reduced ability to synthesize new dopamine in those chronic cannabis users who develop psychotic symptoms, despite having unimpressive specific changes in their numbers of brain DA receptors compared to those users who do not. So, while long-term cannabis use causes changes in the DA system in psychosis, there are not necessarily the changes we might have predicted.

Overall, the neuroscience of cannabinoid dependence is still in its infancy. At Yale, Deepak Cyril D'Souza[55] used PET scanning techniques similar to those described above to capture images of a radioactive labeled chemical that binds very tightly to CB_1 receptors, enabling their numbers to be tallied. Daily cannabis users, who had been briefly abstinent, showed a 15% reduction in these receptor numbers, suggesting that chronic exposure to cannabis had decreased (or "down-regulated") them, exactly as occurs in animals treated chronically with CB_1 receptor agonists. D'Souza then followed his subjects as outpatients over the next four weeks, checking their urine regularly to ensure they were not relapsing to cannabis use. What he found was that the cannabinoid system "rebooted," and receptor numbers returned to normal levels after about two weeks of abstinence. The two-week period corresponds with what clinicians have observed is the typical time span for cannabis withdrawal symptoms to last. Symptoms generally

emerge after a day or two (unless they are dramatically provoked by giving an antagonist drug such as rimonabant) and are usually gone in a fortnight.

Memory is another domain with heavy ECS involvement. Most people are familiar with the fact that acute cannabis intoxication induces impressive short-term memory deficits. The key brain region involved in this effect is the hippocampus. The structure is a gently curved thumb-sized piece of brain shaped a little like a seahorse. It swims deep on the inside surface of the temporal lobe in each hemisphere. As was shown in the disastrous neurosurgical removal of these areas from the patient HM,[56] the hippocampus is essential for forming episodic memories. These are best described as the recall of information about what you experienced, where it happened, and when it occurred. An example might be where you were when you heard about 9/11. Complex electrophysiological patterns known as "long-term potentiation" (LTP) in the hippocampus are essential to retaining these types of facts. Interfering with this process leads to problems recalling past events and remembering new ones. THC significantly suppresses hippocampal LTP. This phenomenon likely explains some of cannabis's well-known acute memory-impairing properties on short-term recall. As the old joke goes, "If smoking marijuana causes short-term memory loss, then what does smoking marijuana do?"

Consistent with this information, mutant mice bred to lack CB_1 receptors have altered short-term memory, spatial memory, and motor learning.[57,58] Jo Cameron complains that she often loses track of her thoughts in midsentence. An extension of this cannabinoid-memory story comes from a recent study.[33] Two major information highways from the cerebral cortex into the hippocampus carry information about "what happened" and "where did it happen" that are part of the recipe for building a new memory. The time-stamping of memories occurs in the hippocampus via unique "what" circuit labels. Endogenous cannabinoids are essential in creating this signal. This activity is not the only exception to the rule that cannabinoids act as simple neuron "circuit breakers." [59] If that were true, then both "what" and "where" aspects of memory would be equally affected. Other examples abound. CB_1 receptors are found on multiple cell types throughout the brain, and activating them has radically different outcomes, for example on cognition, depending on their location. In other words, our brains' cannabinoid neurotransmitters have very different functions in different brain locations.

Outside of memory and reward, endocannabinoids and CB_1 receptors also have important functions in dealing with emotions and mediating stress response and release of stress-induced neurotransmitters. They also consolidate emotional memories, process threatening stimuli (fear regulation), and manage anxiety.[59–61] Although the ECS clearly plays an important role in regulating these emotional behaviors, manipulating cannabinoid signaling in humans results in complicated and sometimes contradictory effects. That observation is familiar to many of us. Talk to half a dozen of your friends. While the majority will tell you that using cannabis makes them feel calm and relaxed, you can always find somebody who won't use weed because it makes them anxious and may even provoke a panic

attack.

Preliminary evidence implicates cortical CB_1 receptors in various neuropsychiatric disorders. For example, the ECS seems to be significantly altered in Parkinson's disease, multiple sclerosis, seizure disorders, Alzheimer's disease, ALS, major depression, and schizophrenia. Abnormal anandamide levels have been detected in the cerebrospinal fluid of schizophrenia patients. Intriguingly, THC seems to promote psychosis while CBD may have antipsychotic properties.

In summary, the ECS is intimately intertwined with many different types of brain and behavioral functions. The phytocannabinoids in the cannabis plant can be used recreationally to temporarily reset some of these responses (for example, to boost the pleasure of rewards or to reduce anxiety). Some neuropsychiatric disorders seem to involve ECS abnormalities, so by extension, at least logically, cannabinoids of various sorts may be candidates for potential therapies for these conditions.

The extended ECS

In addition to the brain, the ECS extends throughout the entire body. CB_2 receptors are present in bones, the gut, and the immune system (including the spleen, thymus, tonsils, and the surface of immune cells). Some extended ECS activities likely involve widespread coordination of physiology, linking the physical with the mental. For example, both endocannabinoids and phytocannabinoids have well-established effects on appetite. In the brain, THC acts directly on the hypothalamus to increase appetite, hunger, and food intake (the munchies); and it acts in the nucleus accumbens to rebalance food-related reward as well as taste perception. In addition, outside the brain, the ECS helps to regulate metabolism in fat cells and to control important aspects of intestinal function. Many of these linked processes are more complicated than researchers thought initially. For example, counterintuitively, individuals who consume a lot of cannabis tend to lose weight rather than gain it. That observation seems to contradict the practice of providing medical cannabis to stimulate appetite in medically underweight patients (such as those with HIV/AIDS or wasting due to cancerous conditions). Part of this complexity lies in the fact that the relationship of the ECS to appetite and the gut goes way beyond the munchies and is also highly dose dependent. Both CB_1 and CB_2 receptors are present in the intestines in large numbers. The former sense fat as part of their role in regulating appetite, separate from brain effects. The ECS also regulates intestinal movement and controls both how quickly food moves through the gut and how the body's energy balance is regulated. In this latter role, CB_1 receptors help control glucose metabolism, fat breakdown, and energy balance, as well as modulating effects of steroids. Blocking these receptors tends to slow down weight gain. The role of cannabinoids and their receptors on modulating symptoms of nausea and vomiting is likely mediated both through the gut and the brain. This may explain in part the recently reported phenomenon of cannabis hyperemesis syndrome, a condition

where frequent cannabis users experience severe nausea, vomiting, and abdominal pain.[62]

ECS components seem out of balance in numerous gastrointestinal (GI) disorders, such as inflammatory bowel disease, and (somewhat surprisingly) chronic liver disease. CB_1 and CB_2 receptors in the liver seem to have opposite roles. CB_1 overstimulation lards the liver with fat, promotes the formation of scar tissue, and causes liver cells to multiply and then die off prematurely.[44] Conversely, CB_2 receptors have opposite effects on the organ and thus seem to have therapeutic potential for treating chronic liver disorders.

Other organ systems

CB_1 receptors are located in the heart and blood vessels. Their presence explains why cannabis smoking causes people to get bloodshot eyes (through blood vessel dilation) and a speeded-up heart rate. In addition, CB_2 receptors are found in these same locations, where they likely play a role in reducing the inflammation associated with fatty deposit (plaque) formation in coronary artery disease. It is now believed that CB receptors have an important function in the development of common chronic heart-and-blood-vessel disorders,[44] and that overactivity and dysregulation of the ECS underpin injury and inflammation in this system. There is emerging evidence that marijuana use may be associated epidemiologically with the development of coronary artery disease or heart attacks. But this effect is much weaker than the clear and highly significant link for these disorders that accompanies tobacco smoking.

CB receptors are also activated by external energy-related factors. For instance, aerobic exercise causes release of anandamide, which may contribute to “runner’s high” as well as mobilizing energy stores and reducing exercise-related muscle pain.[63] Athletes tend to favor the use of CBD to ease such pain, but no convincing clinical trials have yet been conducted to investigate this possibility. The ECS plays an important role in muscle formation; CB_1 receptors are well represented in muscle cells and play an important role there in managing how muscles budget energy. Cannabinoids also influence bone growth and repair,[44] so it will be important to figure out whether there are effects of THC use in adolescence on height. Maybe pot use gets one less “high” altitude-wise. Research in Israel has begun investigating cannabinoids in bone repair following fractures.

In the reproductive system, CB_1 receptors seem to play a role in fertility, are present in the placenta, and are necessary for embryos to implant normally in the wall of the uterus. This explains some of the concerns regarding deleterious effects of cannabis smoking associated with use immediately before and during pregnancy. CB receptors are also present in the testicles, where they influence sperm production and help orchestrate effects of sex steroid hormones in the reproductive tract.[44,64]

The immune system and inflammation

CB_2 receptors play a major role in immune regulation. First, a little context. The human immune system consists of two distinct parts, the innate and adaptive divisions. The innate immune system is a general-purpose, short-term frontline defense apparatus consisting of a collection of chemicals and proteins that block and destroy bodily invaders. The adaptive immune system is much more specific, recognizing and remembering proteins that don't belong to our own bodies and neutralizing them to prevent infection and disease. This latter more sophisticated system operates through specialized cell classes, including B lymphocytes, whose surfaces are studded with numerous CB_2 receptors. Endocannabinoids and their receptors alter the functional properties of immune cells, and 2-AG helps control when and where these cells are deployed in their miniature search-and-destroy missions. The fact that the ECS seems to be so bound up with immunity has caught the attention of many researchers. Designing novel drugs that are potentially powerful anti-inflammatory agents or can modulate the immune system through ECS-related activity is a hot area in the pharmaceutical community.

Cannabidiol, the "cure-all"

Earlier, we reviewed CBD's complex effects on the ECS. Because this cannabinoid is in the news so much, and so many claims are made regarding its effectiveness in treating various disorders, I would like to spend some time focusing on this compound. CBD is found in both nonintoxicating hemp and THC-containing cannabis plants. One often reads that CBD is free of psychoactive effects, but that's not accurate. It's probably more correct to say that the drug is psychoactive in its ability to reduce anxiety, but that it does not produce intoxication. CBD was present at the level of a few percent in 1960s-style street cannabis, but this amount is now significantly lower as a result of selective breeding to drive up the percentage of THC to obtain more intoxicating cannabis. The logic of the biologic pathways in cannabis trichomes is such that breeding plants for higher THC levels necessarily drives down the amount of CBD and vice versa. When it comes to THC's activity at the CB_1 receptor, the combination of modern high-potency THC and low or almost absent CBD is claimed to be the equivalent of pressing on the gas pedal while taking the foot off the brake, with resulting consequences for psychosis risk. This hypothesis is discussed further in Chapter 6. Cannabidiol has been described as pharmacologically promiscuous because of its wide range of activities and interactions with multiple other neurotransmitter systems.[26] Conventional wisdom holds that CBD is not psychoactive (or at least not intoxicating like THC) and that it opposes THC's effects. All these claims turn out to be more complicated than they appear,[65–67] as we discuss elsewhere. Given the many health claims made about it, the central question is whether CBD is an effective drug, and if so for what conditions?

On the one hand, CBD is a substance that has demonstrated therapeutic potential in diminishing seizure activity in young people with specific types of intractable epilepsy, and possible utility controlling pain and inflammation as well

as reducing symptoms of schizophrenia.[68,69] Beyond this, CBD is also widely touted as being beneficial to one's mind and body in myriad other ways, but the evidence for claims such as its ability to cure insomnia and significantly reduce anxiety[68] are mostly anecdotal at this point, particularly so given the very low doses contained in most consumer CBD products.[70] Essentially, the hype has run way ahead of the evidence, and there is a serious lack of properly controlled clinical trials for most of the purported health benefits claimed for CBD.[71] This is not to pooh-pooh CBD's genuine therapeutic promise and already-demonstrated efficacy in certain conditions.

And as we will explore in Chapter 9, orally administered plant-derived CBD is undoubtedly effective at reducing the frequency of seizures in certain rare, severe childhood epilepsies.[72–77] As a result, in 2018, the CBD drug Epidiolex was approved for treatment of these neurologic conditions by the US Food and Drug Administration. CBD also boosts endocannabinoid tone indirectly through mechanisms that remain somewhat obscure, and counteracts the tendency of the glutamate neurotransmitter system to ramp up excessively in some circumstances and damage neurons. This and other evidence that CBD has antioxidant and anti-inflammatory properties suggests that it may have neuroprotective properties.

Other important interactions of THC and CBD occur in and around psychosis. Outside of its subjective effects such as feeling "stoned," "chilled out," or merely "altered," cannabis causes some people to feel paranoid, suspicious, conceptually disorganized, and susceptible to unpleasant sensory distortions.[26] These effects can be easily demonstrated on clinical rating scales that measure psychotic symptoms in individuals with schizophrenia and related disorders. CBD does not produce these psychotic-like symptoms but may have antipsychotic effects, as we will explore elsewhere. Epidemiologic surveys have explored how ratios of CBD to THC influence various symptoms, and pharmacologic studies have administered CBD as an antipsychotic to people with schizophrenia, with variable success. In addition, a handful of human studies have compared the acute effects of THC and CBD interactions in the realm of psychosis. These data suggest that CBD may dilute the tendency of THC to cause psychosis-like symptoms in some people.[26] This claim needs much more study, however, for several reasons. First, chronic psychosis risk is associated with repeated, chronic exposure to marijuana, and most human lab experiments are necessarily limited to acute dosing. Second, in epidemiologic studies out in the community, much of the dosing data relies on participants self-reported cannabis use, which is of variable accuracy. And both the total amounts of cannabinoids consumed as well as THC-CBD ratios are often unknown. Third, despite the increasing popularity of concentrates and vaporizers of various sorts that enable blending of CBD with THC, there are remarkably few lab studies of acutely inhaled CBD. Overall, as summarized recently,[65] the bottom line of how THC and CBD modulate psychotic symptoms likely depends on the ratio of the two drugs, how they are administered (for example, orally, by injection, or by inhalation), how far apart in time they are given (and in what order), and the absolute amounts of each cannabinoid in the doses.

Can CBD get you high?

The traditional answer to the question "Can CBD get you high?" is a firm "No." Conventional wisdom also tells us that CBD significantly modulates and lowers psychoactive effects of THC. Recent experiments carried out by Nadia Solowij and colleagues[65] highlight the potential value of carefully conducted lab studies in puncturing conventional wisdom regarding acute effects of cannabinoids. Solowij examined interactions of various doses of THC and CBD alone and in combination administered to subjects by a vaporizer, compared to placebo. The experiment's main results are very interesting. Contrary to the expectation that CBD would have no psychoactive effects, the high-CBD-dose subjects reported "distinct feelings of depersonalization, derealization and altered internal and external perceptions" compared to placebo. These subjective effects were especially marked soon after dosing and persisted for a couple of hours. In other words, CBD made the research volunteers slightly stoned. Their ratings of intoxication with high-dose CBD were uniformly lower than those resulting from the high THC dose, however. Subjects who received the high CBD dose also appeared objectively intoxicated to the trained research observers, who were unaware of what volunteers had received at each session. This effect of CBD was only apparent in the infrequent cannabis users. More intriguingly, when subjects inhaled the THC-and-low-CBD combination, they self-rated their highness level as being ever so slightly greater than when using the same amount of THC by itself, rather than lower as might be expected. Blood levels of THC also appeared to be increased by the low dose of CBD, suggesting that the small amount of CBD was boosting (albeit only by a tad) rather than diminishing THC's psychoactive effects. Thus, CBD administered at different doses appears to have opposite effects on the high produced by THC. This suggests that medical marijuana patients seeking to offset THC effects (such as intoxication or memory loss) with CBD need to pick their relative doses judiciously, or they may be inadvertently increasing rather than decreasing these side effects. And CBD, at least when inhaled from a vaporizer at relatively high doses, does seem to have acutely intoxicating effects compared to placebo, at least in occasional cannabis users. Another important issue that we are still unsure about is how CBD oil taken orally influences THC effects from smoked marijuana.

Cannabinoid neuroscience—summarizing the evidence

At the beginning of this chapter, I claimed that recent research has contradicted some of our earlier ideas about how the ECS functions. Let's revisit that assertion here. From humble beginnings as research curiosities, seemingly restricted to understanding how we get high from marijuana, endocannabinoids have been described as "among the most widespread and versatile signaling molecules ever discovered." [44] Given its biological roots in CB receptors functioning as a primitive neural coordination system in sea squirts, and with endocannabinoids mysteriously stuffed inside truffles, it is incredible that the human ECS has

evolved into a vastly complicated, ubiquitously distributed coordinating system inside our bodies. It is responsible for so many different kinds of activities in different organs and systems that it is impossible to sum up its many functions in any straightforward way. Rather, let's pick it apart one piece at a time, beginning with the receptor portion of the ECS. As was nicely summarized in a recent comprehensive review,[78] CB_1 receptors have fewer predictable "intrinsic" signaling properties than "typical" GPCRs such as opioid or dopamine receptors; instead, their effects largely "emerge" in a time-dependent manner depending on where the cannabinoid receptors are located. Researchers initially believed that local concentrations of CB_1 sites correlated with the extent of their role in that region, as is typically the case for other neurotransmitter receptors. But the overall number of CB_1 receptors in a particular location turns out to be an unreliable guide to their local importance. For example, in the hypothalamus, receptor cannabinoid numbers are low yet their function is critical, as illustrated by important behavioral consequences and unexpectedly high levels of cannabinoid-dependent signaling. Brain geography also determines what function endocannabinoids subserve. As we saw in the hippocampus, there are opposite consequences of their activity in adjacent territories. Cannabinoid receptors located on different types of brain cells not only interact differently with other neurotransmitter chemicals but also evince multiple behavioral consequences. The more we learn about the ECS, the more it sounds like it makes up the rules as it goes along, depending on the location and the biological task at hand. There are other surprises. Unexpectedly, CB_1 receptors can buddy up with other brain neurotransmitter receptors, as we saw in the case of opioid receptors in the context of pain control. When such concatenation occurs, stimulating the resulting joint receptor elicits a signal very different from that derived from either receptor alone.

Our original simple-minded concept of the ECS was that it acted as a type of modulating "off switch," or "circuit breaker," at neural synapses. This view turns out to be overly simplistic. Typically, when we give a large dose of a particular drug, we will see more of the same effect that was produced by a smaller dose. But this is not true for behavioral responses resulting from either stimulating CB_1 receptors or dosing people with exogenous cannabinoids such as THC. In both cases, there can be biphasic opposite effects on anxiety, novelty seeking, fear responses, and food intake. There's a fair amount of evidence that the cannabinoid system interacts mainly with brain-excitation systems at one dose range and with inhibition systems at another, in ways that are consistent for a particular behavior but differ from one behavior to another. Finally, numerous endogenous molecules similar in structure to endocannabinoids are floating about the brain. Although these entities seem to be both biologically active and an integral part of the ECS, their function is essentially unknown. All these molecular features are uncharacteristic of classic neurotransmitter systems. So far, we have a very limited understanding of their purpose, necessity, and biological advantages. These many unexpected findings challenge many dogmatic views in neuroscience in a broad manner that extends well beyond the ECS and serves to remind us that much work

lies ahead before we can fully comprehend this complex, multifunctional system.

In conclusion, this chapter has summarized the discovery of the ECS; its component enzymes, receptors, and neurotransmitters; our growing realization of its medical and behavioral importance; and our continually changing view of its many functions. The whole area of cannabinoid-related research is of intense interest not only to scientists of various stripes but also to pharmaceutical companies, who glimpse the possibilities of designing novel drugs to manipulate this widespread, little-known but vital system in order to help treat a wide range of illnesses.

Chapter 5

PSYCHOLOGY + HUMAN BEHAVIOR

> And I saw anew many of nature's panoramas & landscapes that I'd stared at blindly without even noticing before; through the use of marijuana, awe & detail were made conscious. These perceptions are permanent—any deep aesthetic experience leaves a trace, and an idea of what to look for that can be checked back later.
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> ALLEN GINSBERG, "The Great Marijuana Hoax," 1966[1]

> The brain on marijuana will never deviate from its destined disposition, nor be driven to madness. Marijuana is a mirror reflecting man's deepest thoughts, a magnifying mirror. It's true, but only ever a mirror.
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> CHARLES BAUDELAIRE, *Artificial Paradises*, 1860[2]

This chapter deals with some essential questions: What are some of the reasons people use cannabis? Does cannabis enhance creativity? What's it like to be stoned? Why do different individuals have different experiences when they use the drug? How does cannabis affect sexuality? What's the story on cannabis's effects on memory, cognition, and driving ability? How are these experiences related to dose and method of administration? How does what we learned about the endocannabinoid system and brain function help explain some of these experiences? Related issues, including cannabis use and risk for psychosis, the drug's long-term effects on IQ, and the modification of THC-related effects by terpenes, are dealt with in other chapters.

An introduction to intoxication

Let's begin with a big broad, general question. Before we even focus on cannabis, it's important to ask why human beings choose to tinker voluntarily with substances that alter their mental states for recreational purposes. These discussions of cannabis raise much wider issues that apply to the myriad of recreational drugs affecting mood and consciousness, from legal everyday examples such as caffeine, tobacco, and alcohol through the illegal, including ecstasy, marijuana, opioids, and psychedelics. But the prohibition of alcohol in the United States in the 1920s and early '30s illustrates that a drug that is legal one day can become illegal the next. Many of these issues are addressed at length in Richard Davenport-Hines's masterful and comprehensive book *The Pursuit of Oblivion*.[3]

The tendency to intoxicate ourselves for pleasure is far from unique to humans

and bound up with the desire for amusement and diversion. Anthropomorphism be damned. If you don't believe that crows like to entertain themselves, then google the video of a Scandinavian crow sliding down a roof repeatedly on an aluminum plate. Rats divert themselves by playing hide-and-seek.[4] Also, for such spontaneous amusement, many creatures incorporate chemical intoxicants. Elephants seek out and ingest fermented fruit to get drunk, and similarly many birds consume fermented berries that render them so squiffy they fly into windows or stagger around. Despite the many liquor brands named after their kin, they don't actually drink Old Crow or Wild Turkey. As anyone who has smoked really poor-quality cannabis flower can attest, inadvertently included cannabis seeds contain no THC and serve no apparent purpose for the would-be stoner other than to make interesting popping sounds when heated in a joint. Hemp seeds are included in many store-bought wild birdseed mixes, but because of the near-zero available THC content, no birds or animals (such as the bears who raid backyard bird feeders) are known to become intoxicated by consuming the seeds or indeed marijuana plants themselves in the wild. Crows, lemurs, and sundry other beasts share the general desire to alter their states of consciousness. We already encountered the opium-poppy-intoxicated parrots in Chapter 2. Crows rub ants that secrete psychedelic substances into their feathers, while in Madagascar lemurs bite and sniff millipedes that contain toxic mind-bending chemicals. For both bird and mammal, alongside the fact that these chemicals often usefully repel pests, getting buzzed is the goal. And in case you're wondering, given the British expression "stone the crows," it is possible for crows to be intoxicated by cannabis. This experiment was carried out in 1843 by Sir William Brooke O'Shaughnessy, who fed cannabis preparations to crows and observed their subsequent insobriety.[5]

Like the birds and beasts, but provided with something as inherently fragile, uniquely beautiful, and highly evolved as human consciousness, we mortals share a highly developed urge to put the boot in once in a while and to wallop our minds with one of a variety of chemical sledgehammers. Given the multiplicity of neurotransmitter systems that underpin the myriad complex functions of our humanoid brains, there are hundreds of ways to effect such consciousness change. These approaches range from the subtle and featherlight (micro-dosing psychedelics) through the full-on cranial battering ram of cannabis concentrates, all the way to brain-disrupting chemicals such as DMT with the relative wallop of a limited-yield thermonuclear device.

Many of these relevant enabling substances occur in the natural world, the majority within plants and fungi, with a few in more recondite locations such as amphibian secretions. But humans bring two unique and novel aspects to chemical consciousness alteration. The first is a conscious, intentional ability to tinker with these natural substances to boost their effectiveness and to get more pharmaceutical bang for our buck. Given a combination of human ingenuity and a strong push to escape temporarily from our nasty, short, and brutish lives, we've both extracted the key molecules from what the earth provides and more recently

synthesized novel molecular structures that improve on or multiply the effects of whatever Mother Nature created originally. This human chemical ingenuity is a distinct step up from the humble crow, who naturally feels less pressure to escape from the drudgery of working 9–5 jobs or filling out mortgage applications. The second uniquely human aspect is that cultural blessing or its opposite, often alongside legal penalties, attaches to the use of these mind-altering substances. Historically, different societies have made the choice to celebrate or ban alcohol consumption, to glorify or criminalize cannabis use, and to either build religions around or lock people up for the use of hallucinogenic cacti. I would like to focus on just one of these many substances, derived from the familiar cannabis plant. Although of course we will discuss synthetic cannabinoids, these exist mostly on the thermonuclear end of the drug spectrum.

What are motivations for people's use of cannabis?

As with all recreational drugs, motivations for cannabis use are numerous and varied: different people choose to use it for widely disparate purposes and intentions.[6] As Randall Jarrell reminds us, the same water can run a prayer wheel or a turbine.[7] As a parallel with alcohol, a Catholic priest using a tiny amount of communion wine as part of the sacrament, a first-year college student getting wasted on vodka as part of a fraternity initiation, and a skid-row alcoholic with terminal liver disease and delirium tremens are as different from one another as a sadhu using cannabis to contemplate the divine, a wake-and-bake stoner grabbing his first bong hit of the day, and a 75-year-old grandmother delicately nibbling an edible to ease her arthritis pain. Listed further are some typical motivations—an accounting that is not intended to be exhaustive—with my acknowledgment that reasons for cannabis use can vary from one session to another within the same person.

Purposeful controlled recreational intoxication

An example of controlled recreational use is provided by Devendra, our friend at Holi in Chapter 2. Individuals employ cannabis in this manner to get pleasantly stoned, experience mild euphoria, heighten perception, tweak their creativity, better appreciate music or lovemaking, see the pretty colors, and so on. Consistent with this, a very small-scale survey of cannabis use in Canada reported that many subjects use marijuana recreationally "to enhance relaxation and concentration while engaged in leisure activities." [8]

Recreational use taken to an extreme

An example of extreme recreational use is getting trashed as a rite of passage, for example, during spring break in the United States. Employing cannabis in this manner offers a chance to become intoxicated, shed inhibitions, behave outrageously, celebrate, and hook up. Entangled with these motivations is the urge

to rebel, equally applicable to teen tobacco smoking and binge-drinking alcohol. Also bound up with this drive can be a desire to push things to the limit and beyond as part of a personal quest or dangerous journey—in other words, to prove oneself and return safely (hopefully) from the other side. But the uncertainty in that word "hopefully" is part of the thrill for some people.

Specific use to heighten perception, explore one's internal world, and increase creativity

Vikram in Chapter 2 offers one example of this heightened-state motivation. Reaching higher states of consciousness, achieving transcendence, or attaining religious insight most likely represents one of the early uses of cannabis, as we explored previously. Although THC, selected additional cannabinoids, and probably some terpenes undoubtedly possess psychoactive properties, cannabis occupies a kind of middle ground when it comes to defining drugs as psychedelics. Psychedelics are substances that significantly alter everyday perception and conscious experience. Many of them trigger states typically characterized by ego dissolution, derealization, altered sense of time and of the physical body, and sensory distortions including visual hallucinations and synesthesia. Sometimes psychedelics are referred to as "entheogens" because they can induce religious or spiritual states including feelings of oceanic boundlessness, mystical insight, experiencing reality at a new and fundamental level, cosmic unity, awe, ineffability, spiritual revelation, sacredness, ecstasy, and transcendence of time and space.[9] Mescaline/peyote, DMT, LSD, psilocybin / magic mushrooms, and *Salvia divinorum* fall into both categories. Psychedelics are defined variously by what they do (as above) and how they do it (often defined as their acting as agonists at serotonin 5-HT$_{2A}$ receptor sites).

Where does cannabis fit in here? It partly meets the first criterion of being experience-altering, depending on the dose used, and set and setting, but it does not meet the second definition because it acts primarily via cannabinoid, not serotonin, receptors. To an extent that is perhaps underappreciated, however, a small but significant proportion of cannabis users choose the drug as a psychedelic/entheogen, as described in a number of recent publications.[10–14]

Important points emerging from these publications are that psychedelic and spiritual properties of cannabis are dependent both on dose (higher doses are usually necessary) and user intent. So if you don't set out to meet Shiva, then you probably won't. When they occur, cannabis-associated psychedelic effects are generally comparable to those evoked by classic psychedelics such as psilocybin, albeit less powerful.

A recent literature review from the University of Buenos Aires tried to shed light on whether cannabis is psychedelic by analyzing the online Erowid database of psychoactive-substance reports.[15] Examining a total of 165 substances, and using the metric of similarity to lucid dreams, unsurprisingly LSD led the pack of psychedelics. Cannabis, however, came in at a respectable number 5 and was the

only substance in the top 20 that was not classified as a classic hallucinogen. On the other hand, these results are a little puzzling in that hashish and cannabis were very differently classified in these ratings.

Whether or not cannabis increases one's creativity is a hotly disputed and contentious area, in part because measuring creativity in an objective manner is an elusive goal, so that most reports are merely anecdotal. Individuals who have used cannabis to spur their creative process include the writer William S. Burroughs (specifically for *Naked Lunch*); the painter and sculptor Modigliani; the musicians Mezz Mezzrow, Billie Holiday, Snoop Dogg, Bob Marley, and Louis Armstrong; plus Apple's Steve Jobs and the filmmaker Benjamin Dickinson. The general idea is that in the context of amplified emotions and modified thinking patterns, cannabis enables individuals to make new and unexpected connections between ideas more fluidly, to take a looser and more open approach to artistic creation that fosters building bridges between ordinarily unrelated ideas. All of these in turn boost creative originality. One study that tried to probe the interaction between creativity, divergent thinking, and cannabis use[16] had individuals smoke a spliff of their own cannabis and compared them to their own non-intoxicated drug-abstinent baseline. On both occasions, the authors measured performance in a number of psychological domains, including verbal fluency (for example, "How many words can you think of in one minute that begin with the letter 'B'?") and the Remote Associates Test (where subjects were given three words at a time and had to generate a single word related to the original triplet within four minutes). An example here would be being presented with the probe words "night," "wrist," and "stop," with the correct answer being "watch." The only significant effect from cannabis use was found for verbal fluency, where the experimenters concluded that acute use of cannabis boosted divergent thinking only in those individuals who were not particularly creative at baseline.

The association of cannabis with musical creativity either in composition or performance has been much discussed, particularly in the realm of jazz. We should note though that Melissa Etheridge, Snoop Dogg, and Sigur Rós are all engaged in marketing their own cannabis products or are part of related "joint business ventures." One person who explored marijuana and music 20 years ago was Peter Webster.[17] He suggested that a general loosening of associations, desynchronization of thinking, mild interference with memory, and altered time sense are particularly suited in jazz to the need to reimprovise a given piece over time. The slowing of time produced by the drug is claimed to enable jazz musicians to "play between the notes."[18]

Medical use

Legalization of medical cannabis dispensaries often precedes that of recreational use. The list of medical conditions for which cannabis is employed is impressively large. But as a quick guide, the majority of 1,000 customers surveyed at two adult-use dispensaries in Colorado used cannabis to relieve pain (65%) and to promote

sleep (74%).[19]

Misguided self-prescribed psychotherapy

Examples of misguided self-prescribing would be using cannabis to deal with personal problems, frustrations, anxiety, and depression. Users in this category are likely to be more troubled than non-users before they use the drug, and this pre-existing psychopathology contributes at least some part of their motivation to indulge. When cannabis effects wear off, the prior unpleasantness returns, and so this population is more likely to use the drug more frequently; in turn, this type of habitual use enhances the risk of developing new psychopathological problems and of cannabis dependence.

Use of cannabis by individuals in the context of pre-existing serious mental illness—so-called dual diagnosis—is a separate phenomenon. This entire last category of individuals is the one that most concerns policy experts. Their worry is that cannabis will be sold to individuals who will be psychologically harmed by it.

The subjective experience of being stoned

Let's move on to the typical experiences of people intoxicated with cannabis. Immediately we run into several problems. The first is that, with all drugs, individual subjective effects are as unique as individuals themselves, with their different brain chemistries, genetics, personalities, expectations, and prior exposures.[20,21] Going on a roller-coaster ride inside your brain is even more varied than experiencing an actual roller coaster, where there is a limited range of experiences from thrills to incipient nausea and your brain is under your control. In contrast, nobody customarily meets God on a roller coaster or undergoes metaphysical out-of-body experiences. For cannabis, there is a significantly wider spectrum of "typical" encounters with the drug.

A second problem is nicely summarized by Michael Pollan in his essay "Smoking the Toad." [22] This involves the difficulties in trying to describe the inherently indescribable—experiences that include psychedelic drug-provoked encounters of all types. The paradox is that the person describing their altered state is by definition in an altered state and thus no longer an objective observer. Because of their intoxication, the user may not be his or her usual articulate self. Once they are no longer under the influence of the drug, details of the altered state may be hard to recollect accurately. This is partly due to a phenomenon known as "state-dependent memory," where details and memories are most accurately and efficiently recalled when their brain is in the same state as it was when the memory was laid down. An often-cited example is that of Charlie Chaplin in the movie *City Lights*. Chaplin, in his tramp persona, saves a drunken millionaire from jumping to his death, thereby earning his gratitude. Once sober, the millionaire completely fails to recognize Chaplin; but when the former is again inebriated, he immediately recollects the identity of his bosom buddy. So it is with the complex mental states evoked by cannabis intoxication. As soon as a person is stoned, he or

she often immediately recognizes a wealth of thoughts, emotions, and perceptions that elude capture and description when not under the drug's influence. Standard clinical scales that purport to measure marijuana intoxication do a remarkably bad job of capturing its salient characteristics. They rely disproportionately on self-reports of physical phenomena, such as "My mouth is dry right now," or "My heart is beating fast."

Cannabis intoxication is one particular and characteristic example from a diversity of altered states of consciousness that we can potentially sample. Humans are not lab rats, and the complexity of the human brain and the marked individual differences between people argue against there being a single modal one-size-fits-all cannabis experience. In fact, as we see below, there are many varieties. Nevertheless, despite these caveats, the task of describing what people feel when they are stoned is feasible albeit necessarily hedged with many provisos. Some of these potentially distracting influences to take into account include the following:

Expectations and placebo effects

One of the most vivid demonstrations I had of the effects of expectations occurred in medical school. In the class on alcohol use, each student was given a fair-sized glass of a vodka-and-fruit-juice mixture and encouraged to swallow the contents in one gulp. The glasses were wrapped in a vodka-soaked napkin secured with a rubber band. We were told the majority of the tumblers contained two shots of vodka but that some consisted only of juice with a small amount of vodka floated on the top. Between that and the boozy napkin, in the act of swallowing, all of us experienced the smell and taste of alcohol, so it was not obvious who had quaffed the placebo beverage. We then had to rate each other's behavior. The person who was most obviously and stereotypically alcohol-intoxicated staggered around the room, giggling, making inappropriate jokes, slapping everyone on the back, and generally being loud and obnoxious. This was a vast departure from his customary restrained baseline behavior. When we opened the envelopes at the end of the one-hour study, it was revealed that this seemingly alcohol-inebriated young medical student had received placebo. He was familiar with the idea of how people act when drunk and believed that he had received alcohol, so he behaved accordingly. For precisely this reason, most drug-administration studies include a placebo condition and are also performed under double-blind conditions. Thus, any expectations on the part of the experimenter are not conveyed to the subject.

Set and setting: The 1960s LSD-guru Timothy Leary first drew attention to these considerations. The term "set" (an abbreviation for mindset) refers to the physical and mental condition of the person who is receiving the drug at the time they take it—in other words, what they are bringing to the drug rather than what the drug is bringing to them. Mental set includes the individual's personality characteristics, cultural background, mood at the time of dosing, recent experiences, beliefs, current preoccupations, and expectations regarding the

substance. Someone who is depressed, anxious, and upset at the time of cannabis use, or concerned about the risk, will have a different set of experiences than another individual who is calm and relaxed. I tried to incorporate some of these principles into the description of the three revelers and their experiences of cannabis at Holi. Prior experience with the drug likely falls into this category too, as do a series of learning processes subsuming such things as knowing how to titrate one's drug intake to maximize pleasant effects and to minimize any unpleasant ones associated with excessive dosing.

The term "setting" describes the environment in which the person is consuming the drug. This accounts for variables such as physical location, comfort, familiarity, prior associations, who else is there and the degree of social support, and sociocultural factors (is the drug legal or does the culture disapprove of it?). Even room temperature might affect the user's experience. Different social circumstances call for different behaviors when one is intoxicated. Alcohol offers an obvious example. A bunch of businessmen out carousing, celebrating a colleague's birthday by knocking back booze shots in a stripper bar will behave differently than a gaggle of academics delicately sipping sherry with an academic dean at a faculty get-together, although their blood-alcohol concentrations may be identical.

Interindividual biological differences

We are all familiar with individuals who can "hold their liquor" or conversely are "cheap drunks" who become obviously intoxicated after receiving small doses of alcohol. Presumably what accounts for these differences and for parallel effects with cannabis is a host of biological factors. These range from liver enzymes that break down the drug, relevant brain receptors, one's sex, and body weight and percentage of fat (given the fat-solubility of cannabinoids). Some of these metrics are genetically driven. Results of a small experiment examining effects of variation in CB_1 receptor and FAAH genes offer some suggestions that reward responses to marijuana cues are biologically mediated.[20] Additional biology-related factors, including perhaps what you ate prior to using the drug (which might affect absorption of edibles) and configuration of non-cannabinoid brain neurotransmitter systems (such as dopamine, which might influence experiences of paranoia or reward), may all be relevant. I've known individuals who found it impossible to experience the high of marijuana, despite trying various doses and methods of administration, and others who experienced panic attacks and episodes of mild paranoia on first use of the drug that discouraged them from ever trying it again. It seems reasonable that individual differences in biology are determining some of this experiential diversity. Many people seem to have their preferred recreational drug. For some this is cannabis, whereas for others the same substance is at the very bottom of their list. One important biological difference seems to exist for sex or gender. As reviewed recently, women may require lower doses to achieve intoxication and be at greater risk of adverse outcomes from

cannabis use. Men tend to use cannabis more, but in the United States, the sex gap is shrinking. While cannabis use disorder is more prevalent in men, women transition faster from first using the drug to cannabis use disorder. Addiction researchers term this effect "telescoping." Overall though, sex or gender effects are understudied for marijuana use, and this area is ripe for exploration.[23]

Dose: With virtually any drug, including alcohol, effects are dose related, but with cannabis there is an extra layer of complexity. From what we learned earlier, we know some cannabinoid effects are biphasic. For example, low doses of THC may be anxiety relieving, whereas higher doses are anxiety provoking. Dosing also assumes a standard cannabis chemovar, but different ratios of THC or CBD and differential terpene content may be influential in this context. As we'll see later, with cannabis, as with many drugs, new behaviors can emerge at high doses that are not seen at lower ones. A spring shower gently watering the flowers and a monsoon flattening fields and washing away hillsides represent dose effects.

Method of administration: To perform their basic function of extracting oxygen from the air and eliminating carbon dioxide, the inner spaces of the lungs are in intimate contact with the body's blood supply. So, inhaling vaporized or combusted cannabis, or the contents of vape cartridges, is an extremely efficient way of quickly absorbing those chemicals into the body and having them circulate rapidly to the brain. Absorption from the gut, on the other hand, is slower, less efficient, and results in a significantly longer time between taking the drug and feeling its effects. Behavioral consequences of taking edibles are significantly both later appearing and longer lasting than those following inhalation. For inhaled cannabis, onset is within a few minutes and offset within 3 to 4 hours. For edibles, onset is typically an hour or more, with effects lasting anywhere from 5 to 10 hours. Recent studies suggest that dose for dose, use of a vaporizer produces a significantly greater high than smoking the same amount in a joint.[24]

There are also additional considerations in administering cannabis to human volunteers under laboratory conditions. Let's say you want to give precise doses to individuals and ensure that every research participant receives exactly the same amount without some unknown quantity disappearing into the air as occurs with smoking. If that's your goal, then administering intravenous (IV) doses of pure THC may seem appealing. But the method of dosing interacts here with both your subjects' prior experience and the laboratory setting in which the drug is being administered. The average cannabis-using volunteer is most unlikely to have previously received IV THC and probably isn't sure what to expect. Thus, their altered mental set will affect how the drug is experienced. Therefore, the aim of precise dosing has to be balanced against numerous other design factors.

Experience with the drug

There are two separate major effects at work when considering experience with cannabis. The first is that people who are inexperienced with the drug, surprised by its effects or unsure how to titrate and modulate intake, may become

overwhelmed by the experience of intoxication or anxious about what's happening. The second is a metabolically based phenomenon—that of diminishing response or short-term desensitization to successive drug doses. One technical name for this is tachyphylaxis. This effect, alongside the longer-term one of drug tolerance, is due to a variety of biological mechanisms. These include desensitization of brain cannabinoid receptors to the drug, and the liver's homeostatic response of producing more enzymes to break down a substance more effectively when presented with it frequently. Tolerance is one aspect of physical dependence (meaning, needing to use higher and higher doses of the drug to get the same effect). But many people exhibit cannabis tolerance without other symptoms of dependence such as drug withdrawal. These mechanisms explain why the frequent dab users in the Colorado social club, whom we meet later, can inhale enormous amounts of pure THC from concentrates without being massively intoxicated.

Something else that is worth mentioning because it is so characteristic of subjective cannabis intoxication (although its precise mechanism is unknown) is its wavelike nature. Users recount that the "high" feeling fades away periodically, only to well up again unexpectedly. This phenomenon is mentioned by Lester Grinspoon in his well-known book *Marihuana Reconsidered*.[25] One possible explanation for this effect is based purely on the metabolism of THC. The initial hydroxy-metabolite of THC is psychoactive; 11-hydroxy-THC in fact is even more powerfully intoxicating in this regard than the parent delta-9 THC, and more easily gains entry into the brain. So as THC circulates dynamically about the body and is metabolized, one can imagine waves of different psychoactive chemicals periodically cresting and swirling into the brain.

One of the few places where anecdotes perform better than statistics is in exploring subjective drug effects. The next section of this chapter aims to try and capture what "being high" is all about. The researcher who literally wrote the book on cannabis-altered states of consciousness back in 1971 was Charles Tart. His book titled, naturally enough, *On Being Stoned* is available online and is a classic in the genre.[26] Tart elicited information from 150 cannabis users, mostly West Coast college students—an idealistic, serious, and religiously unconventional group. As Tart says, these young people "overcame their fear that the study was a police trap, and so gave of their time and experience." Cumulatively they had used cannabis about thirty-seven thousand times for a total of 421 years of experience. It's worth spending some time reviewing Tart's findings because of his fairly thorough research methods and his attempt to probe a wide variety of possible drug-induced experiences, despite the inherent difficulty of capturing complex subjective journeys. He wanted to catalog information that went beyond the limits of traditional laboratory experiments on the one hand and captured individual, unstructured subjective reports on the other. Tart's approach was straightforward and relied on asking users who had smoked marijuana more than a dozen times to report on cannabis intoxication that they had experienced over the last six months. He used standardized questionnaire items that ranged across almost 20 different

domains of experience. This allowed him to collect a wealth of detailed information that he then boiled down to extract commonalities. He also explored his subjects' backgrounds, encounters with the law related to cannabis use, alcohol consumption, age, educational level, political beliefs, marital status, occupation, and gender. Finally, he documented for each type of subjective experience how intoxicated subjects thought they were at the time. Because those metrics are difficult, subjective, and unreliable to track retrospectively, I've paid significantly less attention to those aspects of his data. So here follows the range of topics that Tart explored and his major findings: I admit to rearranging a few components within categories in minor ways so that, at least from my point of view, like sorts with like a bit more logically. I've done my best to summarize the key points of a three-hundred-page book in a couple of pages, sometimes using Tart's terminology and sometimes paraphrasing, while interspersing my own observations and quotes from Grinspoon and most often from online Erowid users.[27] The Erowid website [28] provides access to a wealth of curated information regarding psychoactive substances, including very detailed user reports. After we review what the cannabis intoxicated think, feel, and experience, we will backtrack into the world of neuroscience to try and explain those findings in terms of how cannabinoids affect the brain.

Perception of the external world: Tart hypothesizes that cannabis alters aspects of perception and distorts interpretation of patterns in the environment that reach the brain through the senses. This is a phenomenon that Grinspoon[25] believes can lead to a subjective feeling of unreality or of the external world being altered or skewed in some way. Tart embeds this phenomenon within a general "reorganization of mental functioning," which to me is a nice encapsulation of what a psychedelic drug does. In the realm of *visual perception*, participants reported seeing objects in sharper contrast, and some experienced people's faces morphing and changing identity as they watched them. They perceived novel hues and could appreciate more subtle shades of color. Visual depth perception altered so that near objects appeared closer and far objects seemed much farther away (an effect that one might be concerned about if driving when intoxicated). Tart quotes one user as saying, "The patterns look awesome. The textures seem richer. The colors seem purer—more vivid—delicious—almost edible! I feel like I'm David Bowman at the end of *2001*—'Jupiter and Beyond.' A very cosmic motif. . . . Also, the artificial synesthetic properties seem to be enhanced—I notice the relationship of the patterns to the music much more than I used to." [29] Some subjects reported Alice-in-Wonderland experiences of objects appearing suddenly huge or tiny. Correspondents told of discerning distinct patterns in normally ambiguous or amorphous visual material such as bumpy wallpaper or cracks in the wall. Some remarked on a sensual quality to their vision, as if their eyes were actually touching the object they observed in some manner. Visual imagery in the mind's eye became more vivid; with their eyes closed, some subjects saw little dancing cartoon figures or richly detailed 3D scenes. With their eyes open, fringes of colored light might surround objects, and some individuals experienced

stroboscopic flickering effects, afterimages, or perceived apparent movement in static objects, especially those in their peripheral vision. As one participant said, “Every time I’d move my eyes, it lagged. Like watching frames of a movie slowly, like flipping through a slideshow. This was amazing, my vision had changed, and my brain was interpreting movement of my eyes differently.” [30] At higher levels of intoxication, inanimate material in the environment such as a heap of blankets might seem to become animated. Frank visual hallucinations unprovoked by anything in the environment (such as participants with their eyes open vividly seeing things that were not there but appeared real) were extremely rare and only occurred at high doses of the drug. To me these latter experiences seem more reminiscent of delirious states.

Hearing: Tart’s students reported being able to perceive more subtle qualities within sounds. They provided examples of musical notes seeming purer and more distinct, rhythm being more prominent, and being able to distinguish words of songs that were unclear or inaudible when they were not high. Along the same lines, spatial separation between various instruments sounded magnified and more 3D, as if they were physically farther apart. These phenomena were experienced as positive and pleasurable. With their eyes closed, students reported that sounds seemed arrayed in auditory space according to their audible characteristics; they also seemed more complex and in some cases provoked visual images. At high levels of intoxication, synesthesia occurred—different notes appeared in various colors or provoked distinct tastes—and serious or complex music was experienced as markedly “sensual and profound.” On a personal level, I recall listening to Karlheinz Stockhausen’s *Stimmung* when stoned at age 20 and being able to understand the piece and to feel it intuitively for the first time.

The whole issue of marijuana’s improving the appreciation and enjoyment of music is much discussed. Anyone who has attended Coachella, a Grateful Dead concert, or a Sigur Rós music performance (where CBD and THC edibles are an intrinsic part of their Icelandic music experience) will appreciate that many cannabis users employ the drug in a general way to “enhance relaxation and concentration while engaged in leisure activities.” [8] Music offers a particularly striking example of this general tendency. When stoned, many people are absorbed in the here and now, are receptive to sounds in the environment, have altered time perception, are in a euphoric and relaxed state where emotions can be exaggerated, are relatively free of mental chatter about the past or future, and are somewhat disinhibited. They are thus free to explore novel implications of environmental events. The combination of these various cannabis-induced experiences seems pretty much designed to increase musical appreciation and enjoyment. In addition, we know from Chapter 3 that harps were discovered in the same ancient Chinese grave sites as cannabis braziers, strongly suggesting use of both simultaneously during funeral processions and ceremonies.

Touch and taste

In the Erowid database of cannabis-use reports, we find some vivid descriptions of altered touch and taste. “Touch becomes more entertaining and far more acute. My ears are more sensitive, sounds become full bodied, and subtleties become easier to distinguish. Music takes on another dimension, it flows from the air, from the walls, the ceiling, from within. Taste, well, I need not say much about that—we all know about the munchies. In short, I become a creature adept at feeling everything to its full capacity.” [31] “I opened up my Snapple and took the most glorious sip of my life. The flavor was exquisite. Raspberry and sugar were orgasmic, and going down, the tea was the most refreshing drink I’ve had to date. My friend lent me some of his sour candies and upon eating them, flashes of light started dancing around in my head.” [32] Surfaces were reported to feel rougher or smoother or more irregular, often in an interesting or entertaining way. Objects felt heavier or lighter; tastes embodied novel qualities; and the experience of eating was more pleasurable. Food not only tasted and smelled better, but these sensations became enhanced and changed for the better in unique and unfamiliar ways. But other reports offer some less enjoyable experiences. “I first noticed that my senses had changed. I was suddenly aware of my socks when I walked. They felt like they had a wrong shape or maybe they were too thick. Anyway walking became something I constantly would notice. The feeling in my fingers also changed, it was as if I had Band-Aids on the fingertips.” [33]

Space and time

Time distortion is one of the most characteristic of cannabis’s effects. A majority of Tart’s subjects remarked that when intoxicated, time passed unusually slowly. For example, a music CD seemed to play for hours, or time even seemed to come to a complete halt, so that experiences were felt as going on “outside of time, or timeless.” Related to this, events seemed located completely in the “here and now,” with intense immediacy and no thought given to the future. Other subjects reported the opposite phenomenon; that is, time seemed abnormally speeded up so that events were over as soon as they had barely begun. Some of his respondents related either that events flowed more smoothly one into the other or alternatively segued jerkily and changed suddenly.

Around 1999, when I worked at Johns Hopkins, our research group conducted an experiment that recruited cannabis-using volunteer subjects to participate in a study consisting of two sessions, a week apart, to record how THC alters time perception.[34] The experiment included each subject going into a PET scanner after we’d injected him or her with mildly radioactive isotope-labeled water to measure brain blood flow. In a double-blind manner, each volunteer swallowed either dronabinol (brand name Marinol), a synthetic form of delta-9 THC, or an identical-appearing placebo capsule. (All of our experiments used placebo controls to deal with expectancy effects.) Dronabinol is a controlled prescription drug approved by the FDA to increase appetite and weight in individuals who’ve lost significant amounts of weight. For example, it is prescribed to people with

HIV/AIDS-associated wasting and to cancer patients to combat the nausea and vomiting caused by chemotherapy. Common sense would tell us that eating a dronabinol capsule should be no different than ingesting an edible such as a marijuana brownie. That was not the case. In fact, when we un-blinded our data to reveal which subject had received which drug on which day, the subjective effects of the active drug were very different from standard descriptions of somebody who had eaten (or smoked) an equivalent amount of cannabis. On standard scales to rate a marijuana "high," our subjects reported variously that the dronabinol made them sleepy, interfered with their ability to think clearly, and made them dizzy or slightly anxious. None of them described being "high," "buzzed," "mellow," or "feeling good." This might represent a consequence of missing entourage effects; pure THC in the absence of other cannabinoids or terpenes produces significantly different psychoactive effects. Similarly, Deepak Cyril D'Souza's subjects at Yale dosed with pure intravenous THC also found the experience rather different from smoking marijuana—and generally not as pleasant.[35]

Back to time estimation. The crucial part of our Johns Hopkins experiment had subjects listen to two tones from a pitch pipe a few seconds apart that were sounded by an experimenter. Subjects then were asked to estimate the time between the notes. This procedure was repeated on multiple occasions throughout the experiment. In some of our subjects, as expected, compared to placebo, the drug caused errors in these time estimates. Other participants, however, were completely unimpaired (in part because dronabinol given by mouth is absorbed very variably from the gut). The most striking temporal distortion effect occurred in one subject, whose first response to the time estimation question was a lengthy pause, followed by the answer "A billion, trillion, quadrillion milliseconds." This estimate was significantly different than the correct answer, which was 3.5 seconds.

Experiences of cannabis intoxication might be difficult to communicate because they seem disconnected from what Tart terms the everyday physical "space/time matrix." Distances were skewed, appearing longer or shorter than they were objectively, especially when walking. Some individuals reported temporary loss of spatial orientation, for example becoming so absorbed in fantasies that they forgot where they were. Others lost bodily awareness and felt their bodies floating in space or actively accelerating through it. Many of the experiences recalled Rod Serling's *Twilight Zone* evocation of realms "as vast as space and as timeless as infinity." Some respondents reported that the space or air around them took on a solid quality and thus was no longer "empty." Space sometimes became defined purely by auditory experiences. At high doses, a small number of subjects described déjà vu feelings, where everything they were experiencing seemed a "rehash" of prior events. Such experiences lead naturally to the next category.

Paranormal phenomena such as ESP

Tart mentions drug-induced credulousness or suspension of disbelief as possibly explaining some paranormal experiences such as ESP. It was the 1960s. A full 76% of his population believed in the reality of ESP, for example, so their collective mental set may have predisposed them to perceiving such phenomena. When intoxicated, they reported feeling very aware of what other people in the environment were thinking, not just in the sense of being more sensitive to subtle cues in their behavior but actually feeling what other people were experiencing with enhanced intuitive and empathic understanding. As one volunteer explained, "I'm tripping on an oblique angle to her mind, so I figure it's about 92% telepathy. I become convinced that what I hear her say is really my mind reconstructing her words into a language I can only understand at a peripheral level. I feel if I could fully understand this language, I could read her mind perfectly. I could gain ultimate insight into the meaning of her speech." [29] Some volunteers reported experiencing magical or psychokinetic abilities while stoned and believed they were capable of performing supernatural operations resulting in direct effects on neighboring objects or people. Instances included beliefs that they could, with 100% accuracy, identify other individuals' astrological signs or predict those people's body movements before they occurred.

Bodily experiences

Some changes in whole-body proprioception seem to be dependent on distraction or inattention, for example, subjects being so absorbed in inner experiences that they failed to notice their own body or where their limbs were located in space. Tart's respondents stated that their bodies felt abnormally heavy, light, larger or smaller, stronger or weaker, or differed somehow from their true body shape. Many subjects described their body feeling unusually light, or sensations of floating in limitless space, or feeling tinglings of energy and power flowing in their bodies. These are experiences that would nowadays be described as a "body high." Out-of-body experiences—perceiving oneself as located outside one's actual physical self from a vantage point in the same room, or far removed in space, or via the mind visiting another dimension and leaving the body behind—generally sum up this type of report. Subjects reported altered pain tolerance, likely related to analgesic effects of both THC and CBD. In addition, some volunteers mentioned either being able to focus on and make pain or other sensations more intense, or to concentrate on other matters and make pain disappear altogether. Touch in some cases became more exciting. A number of subjects reported greatly increased relaxation, or what would now be termed "couch lock." They felt extremely mellow and disinclined to move. In Quebec, the slang for stoned is "gelé," which translates as "frozen." Occasional restlessness was reported. Some respondents reported changes in coordination. Sometimes these were an improvement but more often were a sense of awkwardness and impaired balance. As one volunteer said, "Rather than just doing things and saying things, it was like I was ordering my body to say and do things. I could literally

feel the delay in reaction and the messages coursing through my nervous system. Like I was controlling an organic robot from inside." [36] Some individuals reported that their body shape and the location of their "self" was "messed up." Interior perceptions changed. People became much more conscious of parts of their bodies they were normally unaware of, such as their internal organs, related processes such as heartbeat and breathing, as well as bodily accompaniments of emotion. A handful of individuals have mentioned to me that practicing biofeedback while mildly cannabis intoxicated seemed to be significantly easier for them, both because they were more aware of internal bodily processes and because time was subjectively altered.

Social interaction

Some of the experiences Tart's subjects report in the social-interaction category are clearly due to cognitive alterations—for example, the experience of forgetting the start of a sentence or the start of a conversational thread. What's striking about reports in this category is the variability. For example, some volunteers reported that despite being present at noisy and boisterous social gatherings, they were taciturn. Conversely, others became more sociable, wanting to be with and interact more with others. A number reported that they were disinclined to play ordinary "social games,"—for example, feeling that everyday chitchat seemed hollow and worthless. On the other hand, a number of people reported liking to play elaborate or silly games when stoned. While some individuals characteristically became more distant and objective in their feelings of insight into other people and their social strategies and what motivated them, or "saw them more clearly," others became more empathic. Some subjects became more aware of their value judgments about others. A few became preoccupied by their awareness of how stoned other people thought they were. Tart also reported that while some of his volunteers experienced a greater sense of cohesion and unity with the group or with the world, others felt isolated. These latter individuals reported a "kind of barrier or glass wall between me and the world," along with suspiciousness about companions, or the feeling that others seemed "dead or lifeless" or that their statements were ambiguous. Many also reported a heightening of the overall significance of conversations and events, perceiving that things they and others uttered were more profound, subtle, appropriate, important, and interesting than usual. Likely, much of this variability is explained by set and setting, particularly the baseline personality of the volunteer.

Sexuality

Many of Tart's subjects reported that their sexual drive increased, not in a general sense, but amplified only in situations where they would usually be sexually aroused. Numerous individuals noted that sex was significantly more enjoyable. They attributed this to a heightened sense of touch that incorporated new sensual qualities, with greater awareness of bodily feelings, a focus on the here and now,

and feeling closer to others. At very high levels of intoxication, however, people retreated into themselves, and sexual desire diminished. Several described that when making love they felt in close mental contact with their partner, sharing the experience more, in “a union of souls as well as bodies.” A rare few felt more isolated or distracted by synesthesia. Subjects reported new qualities to orgasm, either more prolonged (possibly an effect of time slowing), ecstatic feelings of energy flowing or exploding throughout the entire body, energy being exchanged with their sexual partner, or total, undistracted immersion in the experience. Others commented on feeling that they were a better lover than when not intoxicated, using descriptions (I’m paraphrasing in some cases here) such as “less inhibited . . . more gentle and giving . . . more sensual . . . more here and now, more confident.”

Cognitive processes: memory

The universal Middle Eastern word for stoned is “mastool.” Its Arabic origin hints at someone with a bucket over their head, but the general meaning is “befuddled and confused.” Within this overall cognitive impairment, memory seems particularly affected. Among Tart’s subjects, there were reports of altered long-term memory; for example, long-ago forgotten events would pop up in consciousness, or subjects spontaneously remembered events they hadn’t recalled in many years. Short-term memory seemed generally impaired (a finding that has now been reproduced many times in research laboratories). Conversation span was shortened, and conversations lost track of, unless effort was exerted. Respondents reported being able to carry on an intelligent conversation (subjectively) despite not being able to remember how the exchange had started, however. Many recorded that thoughts would slip away before they could be grasped, with subjective confusion between thinking of saying something and actually having said it. There were many experiences of state-dependent memory—that is, during the period of intoxication, recalling familiar thoughts or feelings specific to being stoned—that did not pop up in an ordinary state of consciousness (and were unrecalled until next time the person was intoxicated). Some subjects described their memory problems as being due to attention difficulties, such as being easily sidetracked and distractible. Others reported that when sober, they were unable to remember what they had read when stoned. A recent book chapter provides a detailed overall review of short- and long-term effects of cannabis on cognition.[37] A major concern among public-health workers has been the fact that adolescence is the period of statistically greatest risk for beginning regular cannabis use and coincides with significant brain-shaping processes that are theoretically especially vulnerable to neurodevelopmental disruption. This is certainly the case in adolescent lab rats. A review of the literature on cognition in human adolescent cannabis users provides some evidence that earlier and more regular use of the drug is significantly more likely to have adverse cognitive effects on memory, attention, and decision-making. Evidence also documents partial or complete

recovery if people reduce or stop use. Effects on cognition appear to be dose dependent.[38]

Tart's reports are generally borne out by laboratory experiments that we will explore in more detail in Chapter 7. Briefly, cannabis, along with other CB_1 receptor agonists, produces quite marked and frequently replicated acute effects on impairing short-term and working memory in humans. This topic has been reviewed by Deepak Cyril D'Souza and his coworkers at Yale, who have a wealth of experience in this arena.[39] To sum up the large and complex literature, THC impairs all component stages of memory. It has a short-term effect of scrambling an individual's ability both to repeat back (recall) information immediately and to provide information later. For these subjects, the information included such material as stories or lists of words presented to them to remember after they were stoned. The drug didn't affect memory for similar material presented to volunteers before they were given the drug. In addition, the higher the cannabinoid dose, and the longer the wait between administering the material to be remembered and asking the subjects to repeat it back, the worse was the memory problem. Not only are there issues recalling stimuli that had actually made it into the brain, but there are also difficulties getting information in there (what psychologists refer to as "encoding"). This type of memory problem seems to be dependent on several factors, including subjects being distracted. Another memory process, consolidation, that turns labile, transient short-term memories into stronger, longer-term, easily recalled memories is also clearly impaired by cannabis. So not only is short-term recall impaired, but longer-term memories are also harder to access. Finally, when subjects given cannabis try recalling what they had been asked to learn (retrieval), there is intrusion of irrelevant material or items that were incorrect but conceptually related to the stimuli being encoded. For example, if after smoking cannabis you were given a list of tools to remember (hammer, saw, screwdriver, etc.), then you would tend to falsely recall tools that were not on the original list but belonged to the same general category—for example, wrench or crowbar. Cannabinoid effects on memory are almost certainly mediated through the hippocampus in a major way and dependent on CB_1 receptors, since they are reversed by rimonabant.[37,40]

Cognitive processes: thought

Tart's subjects recorded that they became so caught up in thoughts and fantasies that they failed to notice what was going on around them or perceive that another person was talking to them. Their thoughts would drift somewhat aimlessly so that they would experience blank periods. Volunteers would become aware that nothing seemed to have been happening for an extended period. Some individuals reported experiencing spontaneous insights about themselves or how people in the environment conducted themselves socially. As one volunteer said, "Thus, the brain has everything it's ever learned written down and recorded on task-specific discs. That way it doesn't have to keep relearning the stuff it has to deal with

every day. It learns and it stores the information on these strange, organic discs. I can see them, clear as day. The brain has learned these behaviors and somehow it has them all stored away in sections, just like the library has its books stored in sections, from horror fiction through to romance, from science fiction through to mysteries. The brain is exactly the same. It's just a clever learning machine, nothing more." [41]

Many stated that their thinking was entirely limited to the here and now with no thought to the future. Sometimes this lack of distraction gave rise to a sense of additional energy, efficiency, or increased absorption in a task. Thinking itself seemed to be altered; individuals would reflect on a topic in a manner that seemed intuitively correct but didn't follow the usual rules of logic or proceed through the usual intermediate steps of thought. Critical logic seemed weakened, with individuals more willing to accept contradictions or things that didn't entirely make sense, sometimes in creative ways. Subjective feelings about the workings of one's own mind varied considerably, with some individuals feeling that their mind was processing thoughts more efficiently than usual and grasping new insights. Others, however, reported muddy thinking or thoughts eluding capture and uncontrollably slipping away before the person could grasp them. The latter phenomenon seemed dose related. "I get this feeling that my brain constantly tries to predict what it is going to happen, and then when something else happens, I become aware of it, slightly confused, because I thought the thing my brain predicted had actually happened." [33] Salience and meaning were altered, less in the area of logic or correctness but more in the realm of depth and subtlety. Commonplace sayings or conversational topics suddenly seemed to embody new meaning or significance, or to be more important and portentous.

Emotions

A more positive mood is almost universal in cannabis intoxication, sometimes to the point of euphoria, although this effect may diminish at higher drug levels. As an example of set, one can see amplification of any preexisting mood or preference. Obvious instances are that the emotional accompaniments of sensory phenomena are turned up all the way to 11 on the dial. If you like chocolate, then it tastes like manna when stoned. If you love Bach, then joyful passages of his music experienced on cannabis are redolent with bliss, and sad, dramatic music plumbs the depths of wretched despondency. On another dimension of happiness, being silly or childlike, with characteristic giggling, are all frequent occurrences when stoned, even when the situation is not that intrinsically funny. Many of Tart's subjects reported smiling a lot and being more aware of the bodily components of emotion. Depth of emotions increased, so that not only were sentiments felt more strongly, but they affected the person more profoundly. Some individuals reported feelings of love and compassion toward others. Others felt more powerful, capable, or intelligent when stoned. A number of individuals had strongly negative experiences. Acute emotional crises might occur in emotionally

unstable people, or in previously unremarkable individuals harboring worries or doubts, when using cannabis. Such people tend to have their problems amplified by the drug, as can inexperienced users who inadvertently smoke or consume more edibles than they know how to handle and are temporarily frightened by overwhelming experiences of disorientation, bodily distortion, anxiety, paranoia, unreality, or fears of losing control. One subject offered this description: “Waves of paranoia washed over me with sickening frequency. Who were those strange entities I sensed but couldn’t see, lurking in the shadows, beyond the shadows? And what did they want with me? I felt as though it were only a matter of time before one of them might choose to manifest itself and begin the inevitable process of reducing me to a gibbering wreck. What could I do to thwart them? Was I losing my mind?” [41]

Control of intoxication

To some extent, because inhibitions are lowered, some individuals welcome their ability when intoxicated to engage in activities that are ordinarily unavailable to them due to anxiety or shyness. Similarly, a tendency to let go and allow fantasies to flow spontaneously, or allow pleasant emotional states to take the user where they will, can be tempered by a conscious push to amplify pleasant or ecstatic experiences. Almost 40% of Tart’s users indicated they had special mental techniques for getting higher. These included focusing on current activity, contact with intoxicated companions, meditation, directly willing themselves to get higher, breathing techniques, music, fantasy, inducing positive emotions, and hypnosis. A very small proportion of his subjects used alcohol to heighten marijuana effects. Loss of control, as mentioned earlier, can sometimes be frightening if the drug experience takes the user into unpleasant territory. One such direction can involve being confronted by or dwelling on realities about oneself or one’s situation that are normally suppressed. Another is the eruption of frightening phenomena from the unconscious. Some of Tart’s subjects (albeit rarely) reported psychosis-like experiences. “I have lost control and been taken over by an outside force or will which is hostile or evil in intent for a while” was one item endorsed. Also rare was the opposite occurrence of being taken over by an “outside force or will which is good or divine, for a while.” As opposed to heightening the drug experience, many individuals who wanted to lessen it and “come down” felt they could accomplish this less via willing it directly but more by indirect strategies. These included inducing negative emotions, focusing on the situation at hand, or pushing themselves to act normally. Obviously, such techniques were less effective at high levels of intoxication, where cannabis had the upper hand and drug effects were harder to combat. When profoundly intoxicated, some individuals used the strategy of attempting to amplify their willingness to trust the situation and “let things happen.”

Identity and spiritual experiences

Tart separates identity and spiritual experiences into two categories, but so many of the events he reports seem to cross boundaries between the two that I collapse them here. As mentioned, whether one achieves spiritual experiences through the use of cannabis likely depends both on the dose and on the user's motivation. Given the well-recorded use of cannabis during ancient religious ceremonies—for example by the Scythians—and during Holi, as well as the current explicit use of cannabis as an essential part of spiritual activities by the Jamaican Rastafari, the fact that the drug evokes psychedelic and spiritual experiences comes as no surprise. Many of Tart's subjects reported changed feelings of self-identity, or "I-ness." Subjects volunteered statements such as "My personality changes so that I'm a different person for a while." They related becoming increasingly introspective and "more like the quintessential me" or their "true self." This alteration seemed to accompany emotional states of openness, such as feeling more childlike, being open to experiences of all kinds, and more filled with wonder and awe at the nature of things. Females had more of these experiences at moderate to strong levels of intoxication. Subjects reported feeling more at one with the world, or being able to focus so strongly on, or becoming so absorbed in contemplating an object or a person's feelings that they became that object or person. One individual reported that he was incorporated into the universal: "Some events become archetypal—part of the basic way man has always done things. That is, instead of me doing something, it is just man doing what man has always done."

Other psychedelic-like experiences included inner voyages and phenomena reported in earlier sections, such as suspension of time, out-of-body experiences, total loss of consciousness of one's body during fantasy trips, and vivid synesthesia. Other subjects reported precognition, telepathy, or the belief that one could perform magic. More straightforward religious experiences included feeling in touch with a higher power or divine being and "feeling more in contact with the spiritual side of things." These occurred primarily at strong to very strong levels of intoxication. Some subjects used the drug to perform activities or enter states that in turn led to religious experiences. Examples included meditating more effectively, being less ego focused or preoccupied with mundane concerns, or more able to center oneself. Some people intentionally used the drug to achieve religious experiences. "To me getting stoned is a communion of sorts with the Godhead." There were rare and more typically psychedelic-like reports of contact with divine beings, or experiencing feelings of unity and oneness with the universe, being part of God's overall plan of things, or becoming "mystically one with the all-knowing." Accompanying such experiences were reports of feeling a high degree of spiritual empathy with others present, stimulation of long-term interest in religion, or emotions of deep peace and joy. Other users experienced "fantasy being as real as reality," out-of-body experiences and seeing or experiencing other universes. Finally, there were reports of mystical sexual experiences such as the dramatic and palpable fusion of souls as well as that of bodies.

Almost 75% of Tart's sample had used more powerful psychedelics such as LSD at least once. Half of that group were "heavy users" of psychedelics, defined as having used more powerful drugs at least a half-dozen times. He attempted to track down effects that were fairly frequent when subjects had previously used powerful psychedelics but were relatively infrequent or rare with pure cannabis users. Experiences that were more common in prior psychedelic users after using cannabis included visual hallucinations, losing touch with one's body and floating in limitless space, seeing another's face transform, and feeling in touch with a higher power. More than half of these psychedelically experienced individuals related that, since having used LSD or another psychedelic drug, they were able to get much higher on cannabis than they had been able to previously. They explained that their psychedelic drug experiences had let them know that certain types of psychedelic experiences were accessible and thereafter used marijuana to attain them. This type of experiential cross-drug transfer is rather interesting but hard to explain.

So the answer to the question "Is cannabis a psychedelic?" is that yes, it can be, especially when taken at higher doses or via edibles, and it is more so in individuals familiar with the effects of "typical" or "classic" psychedelics.

Sleep and dreams

Subjects reported that it was easy to go to sleep following cannabis intoxication, that drowsiness occurred earlier than usual, and that sleep was particularly refreshing with dreams being more vivid than usual. This jibes with the fact that large numbers of medical marijuana consumers choose particular chemovars to aid with insomnia.

After-effects and miscellaneous effects

A few of Tart's participants tended to complain that it could be hard to get organized or accomplish anything the day after smoking. Some disliked that they had poor memory retrospectively for periods of intoxication. And yes, "weed hangovers" are definitely a thing, as shown by early laboratory research.[42]

Dose-related effects

As well as asking individuals what quantities of marijuana they use typically (and where reports are notoriously inaccurate), retrospective inquiries regarding subjective intoxication are important to pursue yet often yield dubious data. As implicit in Tart's account, assigning values to states of cannabis intoxication is important. It would be useful if researchers were able to allot relative quantitative measures to their subjects' levels of intoxication, as well as to compare such results meaningfully with one another. A useful question would be, for example, "How intoxicated did your subjects recall they were when they believed that they could read other people's minds?" Such subjective scales of cannabis intoxication

can range from the very simple, such as visual or verbal analog scales, to the complex and can include both scales of current intoxication and recollections of prior such events. Typically, simpler research instruments ask questions such as "On a scale from 0 to 10, where 0 is not high at all, 5 is how high you ordinarily get, and 10 is the highest on cannabis you've ever been, what number indicates how high you are right now?" One of my favorite nonscientific but nevertheless informative cannabis "highness" scales is to be found at Beyond Chronic. On their "Old Hippie's Levels of Consciousness Scale," 0 is "sober"; 1–2 is "buzzed . . . you can tell you're slightly high, things are more interesting"; 3–4 is "high . . . you tend to stare at objects and into space often, you feel relaxed but somewhat in a daze"; 5–6 is "really high . . . a slight vibration in your body, focusing is hard . . . very random thoughts. Putting together sentences is a challenge"; 7–8 is "blazed/stoned . . . very high, vibrations and waves of euphoria rush through your body . . . mild closed-eye hallucinations . . . everything is brighter"; 9–10 is "in space . . . completely lost in thought, amazing pleasure, you feel like a God . . . sparkling textures everywhere. If you're not standing up . . . don't even try"; 11–12 ranges from "on the verge of tripping" to "you are now tripping. Congratulations and try to hold it together"; 13 is described as "you are tripping and losing control. . . . If you don't manage to keep control at this level, you may well . . . find yourself in an emergency room or mental institution." [43]

The important lesson here is that being stoned is not a unitary phenomenon. Neither is it on a smooth continuum, where more of the same experiences occur in a smoothly graded and completely dose-dependent fashion. It's more of a four-dimensional roller coaster, where qualitatively different and sometimes unexpected phenomena emerge with escalating doses.

Can neuroscience explain cannabis's acute effects?

What might be some explanations at a brain level for the earlier subjective phenomena associated with cannabis intoxication? This is an issue that Charles T. Tart, PhD, would have clearly wondered about. But answering this question almost 50 years later has necessitated a leap forward in neuroscience that was not conceived of in his day. We have learned where endocannabinoid receptors are distributed in the human brain. That certainly provides useful information. But another important question to answer related to the physiological underpinnings of typical cannabis-related experiences and perceptions is which brain parts are switched on or off by acute doses of THC and other cannabinoids. Let's consider observations from both these domains to help address our question of how knowledge of the drug's actions on the ECS health explains what happens when we get "stoned." Much of our understanding of this topic derives from experiments using magnetic resonance imaging (MRI) scanners.

A detour is required at this point to explain how researchers go about collecting different kinds of MRI measurements; multiple kinds of information can be gathered inside the same MRI scanner. *Blood flow* is measured using a technique

known as “arterial spin labeling” that magnetically “tags” water in arterial blood. *BOLD signal* uses functional magnetic resonance imaging (fMRI) to assess a combination of blood flow and metabolism by looking for slight shifts in magnetic properties that accompany oxygen being stripped off hemoglobin in blood cells when these tiny doughnut-shaped corpuscles reach more metabolically active brain regions.

Resting state measures

In typical resting state fMRI studies, volunteers are asked to lie quietly in the MRI scanner for 5–10 minutes, usually with their eyes open, to stay awake, and to think about nothing in particular. Many people intuit that this will yield a signal analogous to a TV not tuned to any channel: a featureless low-key white noise. To most people’s surprise, the brain is always busy, including being highly regionally active during this state of “just spacing out,” and a number of distinct brain networks can be predictably identified thereby. One such network is most active during this “resting state” and is known as the default mode network (DMN). All cerebral networks in fMRI, including this one, are defined simply as groups of brain regions that switch on (or switch off) at the same time and are thus implicitly connected to one other. The DMN is always “on” as a brain circuit, including when we are asleep and even if we are unlucky enough to fall into a coma. The DMN is not unique to humans, and analogues of this circuit are found in our close monkey relatives and even (albeit in a more primitive form) in rats and mice. The DMN is negatively correlated with other networks (that is, its activity is high when theirs is low and vice versa). These half-dozen other non-DMN circuits are known as “task-positive” networks. Their function is related to various ongoing conscious cognitive processes, such as attention, or executive tasks, such as working memory. When the “task-positive” brain networks are needed to participate in a particular activity (like paying attention to something important such as a grizzly bear or remembering items from a shopping list), then circuits related to the task at hand are summoned online. They immediately “wake up” more with regard to their blood flow and metabolism and move to the foreground, activity-wise, while the default mode network flips into the background and lurks there. The component brain regions within the DMN that constitute its “functional hubs” are the posterior cingulate cortex (PCC: located in the brain’s midline toward the back end) plus the precuneus (in the midline part of the brain, toward the back, in the parietal lobe, sitting on top of the PCC), medial prefrontal cortex (also in the brain’s midline, toward the front at about 11 o’clock), and finally the angular gyrus (located on the side of the brain, not in the midline, toward the back and inside the inferior parietal lobule). The individual regions of the DMN are active not only in the resting state during unstructured daydreaming or mind-wandering but also during “internally focused” tasks including thinking about the future, mulling over the past, and autobiographical memories. Changes in resting state functional connectivity among circuits occur in many neuropsychiatric

disorders, but altered relationships either within various circuits (including the DMN) or between different circuits (such as cross talk between the DMN and the executive networks) are easily provoked by any drug that impacts brain function. This of course includes cannabis. There is increasing evidence that these altered within- and between-circuit relationships might be substance-specific. Some researchers, for example, believe that every brain-changing drug leaves its own characteristic, identifiable "fingerprint" on DMN activity for a variable amount of time. All these considerations will help us in interpreting a number of cannabis-related research reports. An important piece of additional knowledge is that one brain region may participate in multiple cognitive or behavioral activities and sometimes belong to more than one circuit. An analogy might be day laborers who have both roofing and drywall skills; one day they may participate in tiling a roof, the next hanging plasterboard, but you won't find them welding or doing plumbing. So let's examine a few of the more important cannabis brain-imaging studies to see what they discovered.

A significant paper was published in 2011 by a Dutch researcher with the *Rocky Horror Show*–like name of Hendrika H. van Hell.[44] (If she turns out to be a future reviewer of one of my scientific papers or grant proposals, I mean this comment in the friendliest possible way.) Van Hell used an MRI scanner to document which brain regions had greater or lesser blood flow in individuals acutely intoxicated on THC compared to placebo. Brain areas whose flow was most prominently shifted from placebo baseline by the drug included frontal regions (where flow increased on the drug) that are involved in many complex cognitive and emotional processes, and that normally act as a "brake" to set limits on social and reward behaviors. Blood flow was also boosted in the anterior cingulate cortex (ACC). This brain region is related to multiple psychological phenomena, including detecting errors, making choices, monitoring and resolving conflicting situations, evaluating social phenomena, and interpreting pain signals. The ACC is also believed to have a role in conscious awareness and experience, and possibly even with experiencing free will[45] (for more discussion, see Francis Crick's 1995 book, *The Astonishing Hypothesis*). Finally, the insula, associated with awareness of processes going on inside the body as well as modeling where the body and its various parts are in 3D space (proprioception), also showed increased perfusion following cannabis. The insula (from the Latin word for "island") is a large, complicated brain region completely buried inside the temporal lobe. In several other brain areas, cannabis significantly decreased blood flow. These regions included the primary somatosensory cortex, a large, well-defined gray-matter region that records and sorts out sensations of pain, touch, pressure, and temperature. As well, it maps sensory space (what's going on where in the body's world of sensation). Finally, blood flow also significantly decreased in the occipital gyrus, a large swath of cortex at the back of the brain that records and interprets phenomena related to vision, all the way from the most basic (such as perceiving light and dark) up to integrating and making sense of complex visual scenes.

Among the functional MRI measurements, cannabis increased signal fluctuations in the resting brain in the cerebellum, right insula, and substantia nigra —areas that are packed full of cannabinoid CB_1 receptors.[40] We discussed the insula above. The substantia nigra (Latin for "black substance") is one of the brain's major dopamine-producing areas and is situated in the midbrain, underneath the main cortical areas at the back of the head. Many of its cells send signals to the basal ganglia, large buried gray-matter lumps that are related to planning and facilitating body movements (especially eye movement) but are also concerned with more complicated functions including aspects of learning and emotion, particularly reward seeking. The substantia nigra probably has a role in REM sleep,[46] related to dreaming.

A second, separate resting state fMRI study[47] also examined the effects of acute cannabis smoking (compared to a drug-abstinent baseline rather than placebo) and found that during intoxication our friend the default mode network (DMN) was transiently highly connected with parts of the cortex linked to hearing and motor movement, while simultaneously significantly negatively connected to the cerebellum and basal ganglia. The presence of this brain state was associated both with the subjects' ratings of altered perception and blood THC levels when they were intoxicated. We mentioned the basal ganglia in the prior paragraph, but now we need to say a word or two about the cerebellum. The structure, which resembles a large piece of pink broccoli, or a lemon-sized mini-brain sitting in the back of the skull, deals with movement control and integration, including learning motor movements and balancing one's posture. Evidence also implicates it in cognitive domains such as attention and language as well as modulating rewards, pleasure, and fear.[48] The cerebellum is also intimately involved in our ability to estimate time, so-called mental timekeeping.[49] Time stamping of memories occurs in the hippocampus, yet another region that is teeming with CB_1 receptors but was not implicated in van Hell's MRI studies.

Eight years later, and in a fresh group of research volunteers, van Hell's group repeated important aspects of their earlier study.[50,51] They recaptured many of their earlier findings. A new discovery was that of increased blood flow in the left middle orbital-frontal gyrus (MOFG), a brain region involved in making decisions about rewards in the environment, figuring out contexts, and calculating the subjective value of rewards. When subjects were stoned, the MOFG was also less connected to the default mode network. THC also increased neural activity in the brain's salience network that detects important stimuli inside the body and in the external environment in order to guide behavior and self-awareness.

Some of you are likely already keeping a mental scorecard of what particular brain regions and their functions are speculatively linked to particular marijuana drug effects. We will get to that topic in a paragraph or two, so I beg your patience here.

Other research groups have conducted similar investigations, often with slightly different designs, and have reached somewhat similar conclusions.[51–55] Other investigations reported more findings, such as altered functional connections

between DMN and insula that correlated with amount of cannabis use,[56] increased correlation between cerebellum and inferior parietal lobule,[57] and that depersonalization after cannabis administration was related to increased activity in the anterior cingulate cortex.[58]

Resting state fMRI studies can be enormously informative about what's going on in the default mode network and the other brain circuits to which it's connected. If we want to learn more about the brain in action when engaged with cognitive tasks such as memory or reacting to different kinds of emotions, however, then a more appropriate experimental design is to have the research subject perform a related task paradigm (such as learning a list of words or watching faces with different emotional expressions) when they are inside the scanner. Without getting into the complexities of how to design and interpret such paradigms, let's quickly review a handful of such task-based studies performed on subjects under the influence of cannabis to gain an additional perspective on how the drug alters brain activity in cognitive-related circuits.

Healthy control subjects in one experiment underwent a learning task that involved reacting to threatening stimuli after being given placebo or a pill containing THC.[59] THC increased activation in the amygdala and part of the prefrontal cortex during the task. Subjects given the drug performed more poorly when tested one day later, and after one week those given THC on the test day showed altered responses to the test cues in these and other regions. In brief, subjects responded differently to the threatening stimuli when acutely stoned, and their brain circuits had learned to perform a task that involved recalling these cues that involved alternative brain regions. This experiment demonstrates THC's effects on an active memory challenge, unlike the resting state studies, and clearly implicates functional alterations in the hippocampus, an area rich in CB_1 receptors and intimately concerned with memory. It also highlighted regions that we have already seen are impacted by THC at rest. In task-related studies, the hippocampus also appears in other contexts related to emotions and to psychotic symptoms. One group studied individuals who either did or did not experience transient psychotic symptoms such as paranoia and anxiety when they used the drug.[60] All subjects activated the hippocampus during the learning task as expected, but in the placebo condition the left hippocampus was much more "switched on" when learning the list of test items in the psychosis-prone individuals. The un-stoned baseline brain activity in their left hippocampus during memory formation was somehow linked with the tendency to experience temporary paranoia when stoned.

Now, as I promised, let's take a look at all these brain-imaging findings, especially those involving the regions most commonly implicated, and what we know about their functional relevance in relationship to what Tart and Grinspoon had to say about the major subjective categories associated with feeling high. An important caveat is that all brain regions are connected to one other, and the brain is organized in circuits rather than a series of isolated areas.

- *Perception of the external world*: Alterations and distortions here are likely

associated with changes in the anterior cingulate cortex through its role in mediating perceptual errors; the insula gives information in terms of where the body is in 3D space, as well as integrating internal and external bodily information. The primary somatosensory cortex integrates information regarding spatial perception and sensory information from the external world, while the occipital/visual cortex mediates all aspects of visual perception.

- *Visual perception*: These changes are likely primarily mediated through the occipital/visual cortex and contributed by the anterior cingulate cortex, with its error-detection function and separate effects on visual tracking through the cerebellum and basal ganglia.
- *Hearing*: Alterations occur in processes mediated by the auditory cortex, and this region specifically, as well as the temporal lobe in which it resides, are clearly affected by cannabis intoxication.
- *Touch, temperature, and taste*: The anterior cingulate cortex helps interpret pain stimuli, as does the insula in its role of dealing with awareness of events and processes occurring inside the body (including pain and temperature perception). The primary somatosensory cortex deals with pain, touch, and temperature information. Likely all these regions contribute to altered perceptual experiences in these realms of consciousness.
- *Space and time*: Spatial awareness is contributed to variously by conversations among the insula, primary somatosensory cortex, cerebellum, and hippocampus, as well as, importantly, by the anterior cingulate cortex (which distinguishes perceptual errors). The inferior parietal lobule is a region that helps integrate the bits and bobs of incoming sensory experiences at a higher-order level to help make sense of them. The cerebellum with its role in attention and mental timekeeping likely plays a major role in subjective alterations in the passage of time. A portion of the substantia nigra is also activated during time reproduction, however, and if it is damaged, mental timekeeping becomes inaccurate. So this “black substance” in the midbrain that is altered by cannabis likely plays an additional role in altered time perception. Finally, the frontal lobe is responsible for much of the ever-present mental chatter (or what Buddhists term “monkey mind”) about the past and future. This is the process that mindfulness advocates urge us to suppress in order to fully experience the present. Cannabis seems to be able to stop parts of these executive processes in their tracks, thus providing a mental shove into the here and now.
- *Paranormal phenomena / ESP*: The manner whereby the experience of these types of phenomena is coded in the brain is presumably extremely complicated and pretty much unknown. Since many people would question whether such phenomena actually exist to begin with, explaining how cannabis can convince individuals of their presence may be a fool’s errand, or perhaps an epiphenomenon of ’60s and ’70s mystical thinking. On the other hand,

paranormal phenomena may be consequences of our being tricked by our own brain processes. In that case, they are potentially amenable to study in the same manner as illusions. Cannabis's ability to reduce the anterior cingulate cortex's function of error detection and distinguishing real from unreal phenomena, as well as the frontal lobe's role in mediating aspects of reality, likely underpin some of these experiences. When combined with some of the earlier-listed perceptual and timing distortions, all may be contributing to this category. Speculatively, if you are thinking less critically, "in the moment," and your sense of timing is disturbed, then you may be more easily persuaded, for example, that you thought of an event a short while before it occurred rather than immediately after.

- *Bodily experiences*: If when stoned you are becoming increasingly aware of your heart beating in your chest and a little unsure of where your limbs are in space, then your insula and parietal lobe are likely being influenced by THC. The insula and its connections are the core brain circuit that interprets bodily awareness (such as paying attention to one's heart rate and internal sensations). The inferior parietal lobe integrates some of these experiences with what is occurring in the environment. Impaired balance is likely mediated through disturbances in the cerebellum, which plays an important role in motor feedback. Part of the substantia nigra, however, also has an important (although indirect) role in dopamine-related motor feedback to the basal ganglia and in helping regulate moment-to-moment motor planning. Examples of its important role in motor regulation can be seen when it is damaged in Parkinson's disease.
- *Social interaction*: The anterior cingulate cortex helps evaluate social phenomena, and prefrontal regions encode many socially relevant phenomena.
- *Sexuality*: Increased pleasure or reward through interactions with the orbitofrontal cortex and the hypothalamus, increased tactile sensitivity (sensory cortex), and generalized disinhibition mediated through parts of the frontal cortex all likely play a role here.
- *Cognitive processes—memory*: The hippocampus is intimately involved with memory formation and is clearly compromised by exogenous cannabinoids. We have discussed the role of cannabinoids in long-term potentiation processes related to memory construction inside the hippocampus and their dependence on anandamide and other endocannabinoids. CB_1 agonists such as THC seem to impair this and related functions, leading to impairment of memory encoding, consolidation, and retrieval.
- *Cognitive processes—thought*: The frontal lobe and anterior cingulate cortex, with its connection to conscious awareness, probably play an important role in this phenomenon. If one is concentrating less on the future, and some of the brakes are off when it comes to logical linear thinking (both effects of mild frontal-lobe impairment), then these processes may account for some of the subjective reports of altered thinking.

- *Moods and emotions*: The amygdala handles many types of emotional stimuli and is studded with cannabinoid receptors. Cannabis effects on this region are likely contributing to some of the drug's mood-related effects. The substantia nigra is an important hub of the brain's reward machinery through its connections with other parts of the dopamine-driven limbic system, including the nucleus accumbens and ventral tegmental area. This circuit as a whole is deeply implicated in trafficking in pleasures and rewarding situations. It fires off when new events confound expectations regarding formerly predictable rewarding situations so that updating reward-related learning is one of its more important functions. When potential goodies in the environment are judged to be important (anything from chocolate to dollar bills or attractive individuals), dopamine-based neurons in the substantia nigra switch on. Or, more correctly, they switch on, and as a result we then judge the stimulus as important or rewarding. The entire circuit is also relevant to addictive behaviors. Parts of the orbitofrontal cortex are also clearly related to reward, and this region's more distant connections to reward-related regions are likely relevant here also in being altered by cannabis.
    - Beyond the world of human neuroimaging, a recent paper from neuroscientists in London, Ontario, used electrical recordings from neurons in the brains of live rats to parse anatomically rewarding versus unpleasant, avoided experiences provoked by THC.[61] The two opposite types of experiences were found to be coded in separate regions of a key reward area the nucleus accumbens. Pleasant experiences localized to its front part, and nasty ones to the rear. THC's rewarding effects in these two adjacent regions were also dependent on different types of local opioid receptors, with the resulting output modulating limbic dopamine levels as a kind of brain seesaw. (This finding is consistent with many of the cannabinoid interactions with other neurotransmitter systems we've seen previously.) Translating these ratty results to the human world, the innate baseline receptor balance between the two parts of the nucleus accumbens may help explain why some individuals tilt toward bliss and others toward anxious paranoia when using cannabis. Related to the involvement of opioid receptors, at various times hashish and opium combinations have been fairly popular. Varieties of "opiated dope" circulated in Baltimore in the late 1970s, and 19th-century French literary types with their exaggerated descriptions of cannabis's effects also favored the combo. It's feasible that an optimal proportion of mu receptor agonists (such as opioids) plus THC would tweak the latter's euphoria-inducing properties. This is a hypothesis that could be tested in a human behavior laboratory.
- *Control of intoxication*: The frontal lobe's "brake" function is the most likely suspect when it comes to exerting temporary voluntary control and setting limits over intoxication, although this ability may be overwhelmed at higher drug doses. Many people who have used cannabis report being able to pull out of the "high" if they need suddenly to do something important that requires

their immediate attention. (“No Officer, I have not been smoking marijuana.”) Van Hell’s functional MRI study documented that cannabis-related blood-perfusion changes in the frontal cortex correlated negatively with her subjects’ self-reported ratings of feeling high. She interpreted this observation as an interaction or tension between cognitive control and drug effect. In other words, this more highly developed brain region was able to figuratively step in and put a brake on the experience of cannabis intoxication when required to by circumstances. In some ways this is analogous to voluntarily waking oneself up from a state of drowsiness if necessary.

- *Self-identity and spiritual experiences*: These complex constructs are high-order functions of the brain that are exceptionally hard to parse, and incompletely understood, but portions of both the default mode network and the frontal lobe likely contribute. Given the possible association of depersonalization with cannabis effects on the anterior cingulate cortex, this region is also likely to be involved, in addition to its role in distinguishing real from unreal phenomena. The anterior cingulate’s hypothesized role in conscious awareness and free will may be important also.
- *Sleep and dreams*: The substantia nigra is specifically related to sleep and dreaming, so cannabis effects here are important.

In summary, cannabis produces a wide diversity of behavioral and psychological phenomena, some of which are explained by knowledge of the distribution of cannabinoid receptors in the brain. Many cannabis-related experiences are influenced by set and setting and by drug dose, as well as by method of administration and pharmacologic effects such as tolerance. Experiments with functional MRI suggest how drug-induced alterations in various brain circuits may be associated with feelings and behaviors influenced by the drug. The “happy, hungry, horny” changes effected by the drug, along with perceptual and timekeeping alterations, seem more readily explained than the drug’s effects on more complex and incompletely understood mental functions, such as sense of self and transcendence.

Chapter 6

EPIDEMIOLOGY

> These new data confirm some of our worst fears about marijuana normalization.
>
> KEVIN SABET, president of lobby organization Smart Approaches to Marijuana, in a press release, 2019[1]

> Federal data shows youth marijuana use isn't increasing under legalization.
>
> KYLE JAEGER, Marijuana Moment, 2019[2]

The opposing quotes above are from two pieces published on the same day (August 20, 2019) discussing identical federal data released in the 2018 National Survey on Drug Use and Health.

This chapter examines some cannabis-related questions from large population-level studies and from surveys. Who is using cannabis? Why? How are these nationwide trends changing over time? What does epidemiology have to tell us about cannabis and risk for psychosis, cannabis dependence, IQ decrements, lung cancer, violence, and motor vehicle accidents? Who is at risk for these problems? Is cannabis a gateway drug? How are these trends likely to change if the United States decides on nationwide legalization of recreational marijuana?

Cannabis is the world's most commonly used illicit substance. One in seven US adults, in a nationally representative survey of over 16,000, said they had used marijuana in 2017, while almost 9% said they had used the drug in the past 30 days. Notably, 20% reported using marijuana in the prior year if they lived in a state where recreational use was legal, versus 12% in states where neither medical nor recreational cannabis was allowed.[3] Breaking down use by administration method, almost 13% of the population reported smoking marijuana; 6% consumed edibles; almost 5% vaped; and close to 2% said they had used concentrates. Focusing only on those who used, over half (55%) preferred smoking. Extrapolating these numbers to the US teen and adult population, around 37.5 million US individuals reported past-year use and approximately 24 million endorsed use in the past month.

Meanwhile, a huge social experiment and epidemiologists' dream come true is going on over the border in Canada since legalization occurred in October 2018. It's early to divine much at this point, but this is a venture akin to the ending of alcohol prohibition that is being intensely studied in the United States to help guide social policy over here.

Epidemiology as a branch of science can be tremendously useful in answering

questions on a population level that are not otherwise addressable. For example, if schizophrenia usually occurs in one in one hundred people in the population, and cannabis smoking in adolescence theoretically doubles this risk, then you will still need to study thousands of adolescents to find a sufficient number who have or have not smoked cannabis, and follow them along to see who ultimately develops this rather uncommon illness. In very basic terms, epidemiologists perform these kinds of investigations in defined populations (such as all young adults in a particular city) to figure out, among other agendas, who develops particular illnesses (for example, men), when (for example, in adolescence or old age), and where (for example, in close proximity to a toxic waste dump). Once the epidemiologists have gathered this basic information, they can estimate such things as how many people in their population are starting to develop a disorder, how many already have it, and what risk factors for the disorder might be. This information is important because it can identify, for example, who's getting sick and where and thus direct treatment resources appropriately, stop an epidemic, or signal that social policy changes need to be initiated.

One technique employed by epidemiologists is to follow a large population of individuals (termed a "cohort") over time and carefully document what's happening with them. For example, a cohort could consist of individuals at increased risk for a particular disorder such as Alzheimer's disease, picked because they had a parent with the disorder; another example would be all the children born in one week in a particular country, followed from birth to see who develops which disorders as an adult.

The pleasant harbor city of Dunedin in New Zealand is named after the Scottish Gaelic name for Edinburgh, the capital of Scotland from which many of Dunedin's early immigrants derived, lured by an 1860s gold rush. As one of the main cities in New Zealand, Dunedin was selected by epidemiologists for a birth cohort study of over a thousand infants back in 1972–73. This multidisciplinary health and development study is still running.[4] Whereas most longitudinal study investigators consider themselves lucky if they can get 70% of their participants to follow up long-term, an extraordinary 96% of the Dunedin cohort's 38-year-olds showed up for their 2011 assessment. At this point, only about one-third of the original cohort still live in the city. But for the study, the epidemiologists gather the participants from the four corners of the earth and transport them back to Dunedin for each wave of follow-up. These check-ins occurred initially every two years from ages 3 to 15, then at ages 18, 21, 26, 32, and 38. The Dunedin epidemiology study is important in its intersection with the world of cannabis in two major respects. First, since the children were studied many years before they began to use cannabis, we know what they were like in terms of IQ, personality, and mental health prior to drug use. Second, their drug use has been tracked fairly carefully. Thus the epidemiologists can speak with some authority on the relationship between youthful cannabis use and subsequent effects, including risk for developing psychotic illnesses, and the drug's relationship to IQ. We will return to both these issues a little later in this chapter.

Because circumstances are changing so rapidly in the United States with regard to cannabis, epidemiology is our most useful tool to track the altered use rates and resulting consequences, such as dependence, motor vehicle accidents, or emergency-room visits. Cannabis is significantly more available than two decades ago because its use has been legalized or decriminalized in multiple states. California legalized medical cannabis in 1996, followed by more than 30 subsequent states. Colorado and Washington legalized recreational marijuana in 2012, followed by another dozen states. Not only is cannabis more available, but also over the last 20 years, it has been viewed as increasingly harmless and thus more acceptable: consequently use has increased.[5]

One might think that it would be straightforward to exploit this natural experiment by comparing states that do and do not legalize marijuana, and quantifying, for example, whether crime or addiction rates change differently in states that legalize. As we see later, however, analyzing these trends is not quite that straightforward.

Deborah Hasin at Columbia University has published much of the important work in this field looking at the number of individuals using cannabis in the United States and the types of problems they experience, based on large epidemiologic surveys. She stresses that "cannabis use is a health behavior that is important to study, just as alcohol consumption is a widely studied health behavior, even though not all persons who drink alcohol have drinking problems."[6] Hasin also mentions some caveats in weighing this type of epidemiologic evidence. For example, epidemiologists often compare US state A, where recreational marijuana was legalized in a particular year, versus adjoining state B, where the drug is still illegal, on such metrics as the change in driving-while-intoxicated arrests, crime rates, or emergency-room visits. Things quickly get complicated, however. For example, such laws can pass in a state on a particular date, but actual marijuana sales may not occur for a year or more thereafter (as happened in Massachusetts). So the epidemiological clock needs to start when the first dispensaries opened—not when the legislators voted. Another issue is that individuals can easily drive over the border from state B to state A, purchase marijuana, and drive back home to consume it, thus diluting any between-state differences. In addition, states may choose to alter how they define driving under the influence of drugs while a study is underway—for example, by initiating blood-test-based limits. When that happens, the statistics for driving under the influence of drugs (DUID) are no longer properly comparable before and after the change in legal definition. (Remember the story about counting pigs at Christmastime.) Another complication is that individuals recruited into epidemiologic studies may report drug use differently after cannabis is legalized. For example, if they now feel cannabis use is more socially acceptable because it's legal, then they may be more inclined to accurately report use. Finally, if recreational marijuana becomes legal and affordable, then use patterns of other recreational drugs such as alcohol may change significantly, and these altered patterns also need to be taken into account by epidemiologists, such as those

studying motor vehicle crashes.

Completeness of relevant information is at a premium. As pointed out by the researchers Prince and Conner, cannabis use is almost always measured by having survey responders report only on use frequency—for example, the number of times or of days that they used during particular time periods (for example, the last seven days or the last six months). Researchers, however, are much less inclined to inquire about the quantity that interviewees used and the drug potency.[7] All three metrics (how much, how often, and what was in it) are likely extremely relevant if one wants to quantify, for example, whether risk for schizophrenia is related to the total amount of THC somebody has used. Epidemiologists need the ability to quantify substance use by employing quantitative measures of such use. For example, for cigarette consumption they employ "pack years" (the number of packs a day you smoked multiplied by the number of years you smoked) to calculate a quantifiable, straightforward measure of lifetime nicotine exposure. For cannabis, a comparable measure is not intuitive. If you buy an ounce of weed from your friendly neighborhood dealer, you're often not exactly sure of the true weight and certainly not clear about the percentage of THC and CBD in your purchase, not to mention other cannabinoids. And, as we will see later, as Prince and Conner showed me in their experiment at the Denver social club, even experienced users are extremely inaccurate in estimating the quantities of cannabis products that they load into a joint or dab rig. With alcohol, measurement of use is very straightforward and translates readily across different types of booze. Alcoholic beverages come in standard-sized bottles. One standard bottle or can of beer, glass of wine, or shot of spirits all equate fairly accurately to a standard alcohol unit. No equivalent metric exists for cannabis, however. That's particularly unfortunate as cannabis potency has tripled since 1995 as a direct result of selective breeding for increased THC content.[8] Another issue is that cannabis consumption often involves sharing a joint or bong with others, making an individual's dose hard to estimate. Recently a couple of researchers from the psychology department at Washington State University came up with an improved survey measure of cannabis consumption that assessed frequency, quantity, and age of onset in detail. Some methodologic improvements included adding pictures of different quantities of cannabis (such as a gram or half a gram) in various forms (such as bud, loose herbal material, and joint). The investigators probed seven different administration methods, from blunts to vaporizers and edibles, clarified personal use (as opposed to sharing), and estimated typical THC levels in the cannabis used. They also recorded use of cannabis concentrates such as oils and waxes. The resulting instrument, now used fairly widely by researchers, is called the Daily Sessions, Frequency, Age of Onset, and Quantity of Cannabis Use Inventory, which conveniently, if cheekily, collapses into the acronym DFAQ-CU (try pronouncing that out loud).[9]

Although it's straightforward to test subjects' urine or hair for cannabis metabolites to confirm that people who tell you they are using marijuana are in fact screening positive for the drug, this is rarely done for reasons of practicality,

expense, and convenience, so we have to rely on people's word in most epidemiologic surveys.

Yet another complicating issue for survey researchers is that because marijuana legalization thus far has been left up to states, with no coordinated federal policy, states are not especially motivated to regulate or define in any coordinated way such issues as cannabis quality control, uniform packaging standards for edibles, warning labels, childproof container use, sale to minors, driving under the influence of cannabis, public consumption, or diagnosed conditions for which medical marijuana is appropriate. This results in a hodgepodge of distinctly different regulations in different states and makes it hard to compare many key metrics such as those regarding DWI or problematic effects resulting from edibles in any consistent manner.

Finally, as we've discussed earlier, correlation (as measured in epidemiologic studies) is not the same as causation. Sales of TVs and rates of motor vehicle accidents may be perfectly correlated, for example (as income levels rise, people can afford to purchase both more cars and more TVs), but TV sales do not cause car crashes. Keeping in mind these numerous caveats, let's take a look at some of the more important cannabis-related findings unearthed by epidemiologists.

How many people are using cannabis regularly? What percent of adults and teens are using, and for what reasons?

Cannabis is now widely used in the United States. In 2016, according to the Center for Behavioral Health Statistics and Quality (CBHSQ), 22.2 million Americans 12 years of age or older reported cannabis use in the past 30 days.[10] New data are now available for one further year, encompassing 2017, and the number of Americans using marijuana rose to 24 million, according to the NSDUH survey (see below). As the perception of risk in using cannabis falls (as it has done steadily), use tends to increase, and currently only 15% of 18- to 25-year-olds view cannabis use as risky. Deborah Hasin and her colleagues examined a very large amount of data from two different phases of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) from 2002 and 2012–13, along with additional survey findings in the general US population such as from the National Survey on Drug Use and Health (NSDUH).[6] They discovered that adult cannabis use had increased over the past decade, and within most sociodemographic subgroups, all over the United States in both rural and urban areas. Both cannabis use and cannabis use disorders grew significantly over this time span, with the biggest increases in men, young adults, Blacks versus whites, low-income groups, the never married, and urban residents. These increases began in 2007. The upward trend in adult and adolescent African American use is notable because it represents an alteration in a long-established pattern of higher use in whites. These data are consistent with earlier reports from the same epidemiological research group at Columbia University, which showed that from 2001 the prevalence of marijuana use had more than doubled (to 9.5%)

over the next decade. Equivalent figures for cannabis use disorder had again almost doubled (to 2.9%) in 2012–13.[11]

Contrary to the fears that underage youth would flock to cannabis, adolescent use in the surveys stayed flat or tended to decrease (from almost 16% down to 13%), with a slight recent uptick for adolescents who were older and nonwhite. For high-school-age adolescents, tobacco and alcohol use decreased over the same time period. Hasin also reported that cannabis use disorder decreased significantly in 12- to 17-year-olds from 4.3% in 2002 to 2.3% in 2014. These latter figures are especially important, as there has been much anxiety expressed among public-health officials and anti-cannabis lobbyists that legalization or decriminalization of cannabis would lead to significantly increased consumption in this biologically vulnerable youth population. It's reassuring both that such increases are not occurring and that medical cannabis legalization does not boost adolescent use, as occurs in adults.[12] Very recent work from other investigators confirms the pattern of continued stable adolescent cannabis use. Hasin also examined this trend in over a million US adolescents in the 8th, 10th, and 12th grades across the years 1991–2014.[13] Although overall cannabis use increased in states that legalized medical marijuana, 8th graders decreased their use, and no significant change occurred in 10th or 12th graders. A recent meta-analysis of 55 studies tracking cannabis use trends found that adolescent marijuana use fails to increase following cannabis legalization. It also helps clarify that prior reports of higher rates of marijuana use among teens in those states is better explained by generally higher rates prior to the passage of medical cannabis laws.[14]

Although cannabis use disorders are growing overall, the risk of dependence formation among heavy marijuana users appears to have declined since 2002. Stephen Davenport at the RAND Corporation analyzed trends in marijuana dependence among daily and near-daily cannabis users, using data assembled from the National Survey on Drug Use and Health (2002–16), to try and determine why the trends had changed. He discovered that dependence among these heavy users fell by 39% over the period studied from 26.5% in 2002–04 to 16.1% in 2014–16. Consistent with the overall result, when he analyzed individual dependence symptoms, most of these also showed significant declines. Examples of such symptoms included reducing important activities because of cannabis use; using the drug despite emotional, mental, or physical problems; failing attempts to cut back; spending lots of time obtaining, using, or recovering from marijuana; and failing to follow through on limits set on use. It's hard to explain these data, but possible explanations include destigmatization of cannabis use, greater legal access (presumably people spend less time skulking around tracking down their dealer), improved product quality and consistency, or perhaps use of edibles or vaporizers (leading to reduced smoking and use with tobacco). The more cynical possibility is that individuals were just less likely to detect their own cannabis-associated problems or to report them in the survey.[15]

A few updates. Everybody from legislators to psychiatrists to epidemiologists is concerned about the effects of cannabis legalization on adolescent consumption.

In general, usage trends in youth have been reassuring. For example, at the July 2019 Research Society on Marijuana third annual meeting,[16] Silvia Martins from Columbia University reviewed recent unpublished data derived from analysis of NSDUH surveys between 2008 and 2016 examining the impact of marijuana legalization in Colorado, Washington, Arkansas, and Oregon, starting with Colorado's legalization in 2012. Past month and daily use of cannabis stayed close to flat in 12- to 17-year-olds, 18- to 25-year-olds, and those older than 26, as did rates of past year cannabis use disorder, except in the 12- to 17-year-olds, where there was a small, hard-to-interpret increase from 22.8% to 27.2%. An analysis within high schoolers across all states showed slight decreases in most grades post-legalization, with a very small increase in 12th graders, particularly among those who worked (who may have access to increased funds). Youth were also more likely to use cannabis if they lived closer to a dispensary and if they were exposed to cannabis advertisements,[17] observations that are useful to guide social policymakers.

Because increasing numbers of people use marijuana to help treat medical conditions, it's important to know who these individuals are, how they are using (edibles, smoking) and how much, and what clinical conditions they are trying to ameliorate. Two Nebraska researchers recently surveyed over 169,000 individuals, half of them women, representing the US adult population.[18] Not unexpectedly, adults who reported medical conditions were more likely both to have used cannabis once or more in the last month and to have used more than 20 out of 30 days in that month. Adults aged 18–24 had the highest prevalence of current use irrespective of medical conditions—more than 10 times higher than those aged 65 and older. Among people surveyed who had medical conditions, 11% of young adults reported using cannabis on a daily basis. Overall, adults with medical conditions were almost twice as likely to be using the drug. Those who did were less likely to report using cannabis for recreational purposes. Rates of medical use varied widely among different US states, with Alaska's being the highest. There, 38% of adults aged 18–34 with medical conditions were users. The biggest medical cannabis consumers were those with multiple medical conditions, and those illnesses, as stated by the patients, included arthritis (64%), skin cancer (62%), kidney disease (57%), stroke (54%), diabetes (52%), and heart attack or coronary artery disease (each around 50%). Remember that many patients had multiple medical illnesses and used medical cannabis to treat more than one condition, which means these totals exceed 100% by severalfold. Somewhat puzzlingly, asthma (46%) and chronic obstructive pulmonary disease (COPD: 44%) were also commonly given as reasons for use, as was depression (49%). The survey raises more questions than it can answer. Were diabetic users employing medical marijuana to help treat the nerve pain which is commonly found in the disorder? Was the depression improved by marijuana use or made worse (as has been reported in some surveys)? The overwhelming majority of COPD subjects (82% of them) smoked their medical cannabis. Was the drug helping improve their condition (unlikely), or making it worse by irritating their lungs?

Large-scale studies with the ability to survey hundreds of thousands of individuals who mirror the population at large are incredibly useful in documenting national trends and allowing epidemiologists to draw broad, generalizable conclusions. That's not to say that small-scale studies lack usefulness, but such supplementary survey information must necessarily be weighed very differently. Some such data are derived from commercial cannabis companies surveying their customers; despite their small size, such studies are interesting because they can shed light on emerging trends in close to real time. For example, in Canada, Canopy Growth Corporation and Tilray tracked several hundred seniors. These studies, and those in the western United States, suggest that older people comprise around 25% of the overall number of cannabis consumers. The Canadian data pick up an emerging trend not reflected in the US national survey earlier: senior citizens are overcoming their doubts and embracing medical cannabis use. These older baby boomers used weed in their youth and now seem attracted to legal cannabis for its medical benefits—for arthritis and other painful conditions, insomnia, and various chronic health issues.[19] Similarly, a survey commissioned by the Colorado Department of Public Health and Environment examined past-year cannabis use in 274 community-dwelling residents aged over 60 years. The mean age of their sample was 72.5, with two-thirds being women. Startlingly, 45% reported past-year use, of whom over half reported using cannabis for both medical and recreational purposes. Reasons for use included arthritis, chronic back pain, anxiety, and depression. Users reported improved overall health, quality of life, day-to-day functioning, and improvement in pain. Those who had used opioids in the past year were more likely to belong to the cannabis user group, likely related to chronically painful conditions.[20] Another small-scale Canadian survey from Kantar Consulting reported that although only 13% of surveyed Canadians report frequent cannabis use, half of those who do are millennials aged 22–39 years.[21]

Schizophrenia: epidemiologic studies

As we will explore later, cannabis use by young people seems to raise the odds that transient psychotic symptoms such as hallucinations and delusions will develop, as well as boost the risk for more chronic psychotic illnesses such as schizophrenia. To put things in perspective, only 1 in 100 people develop schizophrenia, and most young cannabis smokers never develop any psychotic illness. So an important question is "Which cannabis users are at particular risk of developing psychosis?" Epidemiology can help address such questions.[22] As clearly argued by investigators at Yale,[23] as a schizophrenia risk factor, cannabis meets many of the necessary criteria for a causal agent, just as cigarette smoking does for developing lung cancer. These half-dozen criteria include timing (cannabis use occurs prior to development of psychosis, and adolescent exposure may be more significant) and dose-response relationships (higher-THC cannabis increases risk more). Further evidence includes biological plausibility (as we

reviewed previously, cannabis may alter brain dopamine function, and dopamine is involved with psychosis), experimental evidence (challenging people with CB_1 agonists can provoke psychotic symptoms), consistency (multiple studies all suggest increased risk), and coherence (epidemiologic findings are consistent with lab studies). On the other hand, other factors muddy the bong waters. Psychotic disorders are complicated illnesses that have multiple identified genetic and environmental risk factors; cannabis use is only one among many of the latter. Thus the specificity of cannabis's risk for developing schizophrenia is not likely to be particularly high (unlike its users), although it's certainly significant. We will review many of these points later.

Prospective epidemiological studies that follow their subjects through the age of risk of developing a disorder, and carefully monitor drug use, consistently link cannabis use with increased subsequent risk of both (rare) more serious, chronic schizophrenia-like psychosis and (common) fleeting psychotic symptoms. Early onset of use, daily use of high-potency cannabis, and consuming synthetic cannabinoids seem to carry the greatest risk.[24,25] But let's dive into a few of these studies to see how they reached these conclusions and how well their findings hold up to subsequent replication.

Back in 2002, the New Zealand Dunedin epidemiology team that I alluded to earlier turned their attention to the risk of schizophrenia in their sample of over a thousand individuals. The researchers wanted to resolve the question of whether the increased risk of schizophrenia previously reported by others in cannabis users might be a consequence of psychotic symptoms that existed before the onset of the disorder rather than being due to cannabis. For example, a longitudinal Swedish study of army conscripts back in the 1980s had suggested that adolescent cannabis smoking increased the risk of later schizophrenia, but it left the chicken-and-egg question open.[26] In other words, had these young men recognized the emergence of early psychotic symptoms and then attempted to self-treat with cannabis? Having access to the New Zealand sample that had been studied carefully since age 3 (well before any drug use had begun), where psychiatric symptoms had been assessed every few years, offered the opportunity to unravel that question in a new population. Louise Arseneault led the Dunedin study analysis.[4] She and her coworkers reported that their participants who had used cannabis by age 15 were four times more likely to have developed schizophrenia symptoms by age 26, compared to individuals who had either never used the drug or had used it only once or twice between the ages 15 and 18. The effect was stronger with earlier use. After psychotic symptoms at age 11 were controlled for, the risk for having a schizophrenia-like disorder diagnosed as an adult remained to some extent, but it was no longer statistically significant. The crucial numbers in this study were small; only 25 of the total sample had developed schizophrenia by age 26 (10% of the cannabis users versus 3% of the controls).

These early New Zealand epidemiology data were provocative but left open many questions. Like good researchers, the team kept picking away at the problem. Many teens use cannabis, but few develop schizophrenia. Are some

individuals at particular risk, perhaps for identifiable biological reasons, they wondered? A later 2005 investigation from the Dunedin researchers led by Avshalom (Avi) Caspi,[24] asked the question "Are some individuals genetically predisposed to be vulnerable to cannabis effects in a way that makes them more likely to develop schizophrenia?" Caspi suggested that normal variation in the gene coding for the enzyme COMT (which breaks down dopamine in brain neurons) might influence psychosis risk. A little background on genetics is necessary to unpack these findings. For many common normal variations in our DNA, there are two normally occurring variants that we can think of as "flavors" (these are technically known as "polymorphisms") in the DNA that codes for a particular gene. These "flavors" represent variations in DNA bases. Changing the DNA's base letter can sometimes result in an amino-acid swap whenever the DNA is translated into a protein molecule. The technical name for the DNA difference underpinning such variation is "single nucleotide polymorphism," usually abbreviated to SNP and pronounced "snip." For each of the many possible thousands of SNPs in all our genomes, each of us inherits one copy of one of the variants from one biological parent and a second copy from our other parent. The variation determines which of two amino acids is expressed in the resulting protein chain. Sometimes these swaps make absolutely no difference in how the gene functions; in other cases (so-called functional SNPs), the resulting protein has different physiological properties. It can perform its molecular role either more efficiently, less efficiently, or occasionally not at all. For example, sickle cell disease is due to this type of swap affecting the hemoglobin gene. In the case of the COMT enzyme, at base-pair location 158, the two different amino acids produced by the variant SNPs are valine (usually abbreviated to Val) and methionine (abbreviated to Met). Thus there are three possible "flavors" of COMT: Val-Val, Val-Met, or Met-Met. You may be asking why, out of the thirty thousand or so candidate genes in our genome, the Dunedin investigators would focus on COMT. The logic was based on the following. The COMT gene is located on human chromosome 22q11; a micro-deletion on part of chromosome 22 that contains the DNA for COMT (plus several other genes) results in an uncommon syndrome abbreviated to VCFS. Individuals with the syndrome tend to exhibit facial, heart, IQ, and ENT abnormalities, but relevantly they have about a 40% chance of developing a schizophrenia-like illness, or 40 times the population risk. Second, the COMT gene breaks down dopamine inside neurons, and there is suggestive evidence that excessive amounts of dopamine contribute to the risk of psychosis. And Val-Val and Met-Met flavors of COMT break down dopamine with significantly different levels of efficiency, so the SNP definitely translates into a functional difference. So off the researchers went, drew blood samples from all 26-year-old participants, and genotyped their DNA for the COMT 158 Val-Met variant. As we saw earlier, these individuals had already been assessed for psychosis by Louise Arseneault's team. This time around, the researchers assessed adult cannabis use at ages 21 and 26 to see how often the study participants had used cannabis in the last year.

The results of the analysis were striking. The Val gene variant increased psychosis risk in a striking SNP-variant dose-related manner.[24] Merely having one or other variants of COMT by itself had no bearing on schizophrenia risk. The effect of adolescent cannabis exposure was significant, as seen already in Arseneault's study. But there was a significant interaction between one's COMT profile and cannabis use. The greater the Val "dose," the higher was the risk of schizophrenia that youthful cannabis use posed. Thus, if one had the COMT Met-Met genotype, then the risk of developing a schizophrenia-like illness by age 26 was about 4%, whether or not one had smoked cannabis as a teen. If one possessed the Val-Met genotype, then about 2% of cannabis nonsmokers and about 5% of smokers—not very different numbers—had developed the disorder. But the risk was tending to distribute a tad more toward the Val side. But for those individuals with the Val-Val variant, the findings were remarkable. About 2% of the former teen non-cannabis users were affected with schizophrenia; but among those who had smoked cannabis as a teen, the figure leapt to around 14%. If they had used cannabis as teens, carriers of the COMT valine 158 allele were both much more likely to exhibit psychotic symptoms and more likely to develop a schizophrenia-like disorder, whereas cannabis had no comparable influence on individuals with the Met-Met variant.

These numbers suggested what geneticists call a "gene-environment" interaction; that is, one's particular genetic makeup makes one more (or less) vulnerable to some factor in the environment. For example, ethnically Asian people are more likely to have a particular variant of a gene that breaks down alcohol in a way that produces larger amounts of the mildly toxic chemical acetaldehyde, which causes facial flushing and nausea when they consume alcoholic beverages. In other words, their particular gene variant is lying dormant and undetected until it interacts with something (in this case alcohol) in the environment. When it does so, it manifests as red blotches on the face and upper body, a runaway heart rate and vomiting. In the case of the Dunedin sample, the environmental component of schizophrenia risk was cannabis use, along with the genetic risk factor COMT genotype "flavor."

However neat and convincing this story appears, it has problems. Subsequent attempts at replication in other samples do not reliably reproduce this original finding.[27] When very large genome studies (involving tens of thousands of subjects) search for schizophrenia risk genes, COMT is not among the 140 candidates identified. Similar claims for gene-environmental cannabis risk have been made for SNP polymorphisms in the AKT1 gene and psychosis risk, and these also do not replicate reliably.[27] Overall, no single schizophrenia risk SNP conveys more than a tiny degree of risk for the disorder. The risk from common gene variants such as COMT Val-Met is almost certainly additive, with hundreds of genes each contributing a miniscule amount of vulnerability. Logically then, a striking effect from a single gene variant would be very unlikely. Thus, variations in COMT may be playing some possible role in genetic risk in the cannabis-psychosis story, but it seems unlikely to be as dramatic as that initially reported

from the Dunedin study. An emerging subtlety is that there may be a three-way interaction of COMT polymorphisms, cannabis use, and having been abused as a child.[23–25,28] To summarize: a once promising link in the cannabis-psychosis story seems to have lost much of its initial shine.

There are further complexities in the links between cannabis and psychosis risk. Try the following as a thought experiment. We know that both schizophrenia and substance abuse tend to run in families. This suggests that both have a genetic basis, and indeed risk genes for both conditions have been identified. One theoretical possibility is that the genes conferring risk for the two disorders overlap, so the reason cannabis use and schizophrenia appear to be related is that they share a common underlying (genetic) cause. Thus, this line of argument would suggest that both conditions were caused by the same underlying risk and not that one (cannabis use) was leading to the other (schizophrenia). Although there is some disagreement on this issue, some studies trying to unravel this question have shown that cannabis's risk-increasing effects for psychosis may indeed be explained (in part at least) by a shared genetic predisposition for both schizophrenia and cannabis use.[29]

Another relevant puzzle piece is that ratios of THC to CBD of (illegally sold) cannabis in the United States increased from 14:1 to 80:1 between 1995 and 2014.[8] Recall that as chemovars are bred for higher THC, then CBD percentages necessarily fall. Given the potential role of cannabidiol as an antipsychotic (see Chapter 9), some have claimed that this altered THC:CBD ratio, in addition to the role of increasing THC concentrations, is one factor driving increased cannabis-associated psychosis risk.[30] So the next epidemiologic study we examine focuses on that particular issue: is the amount of THC in smoked cannabis, as well as how often cannabis is smoked, relevant to the risk of developing schizophrenia?

Marta Di Forti is part of a large team of epidemiologists, statisticians, and clinical psychiatrists with expertise in psychosis based at the Institute of Psychiatry and the Maudsley Hospital, both in London, United Kingdom. The research group includes Robin Murray (now Sir Robin), a prominent psychiatric researcher who has been hunting down the relationship between cannabis and psychosis for the past 25 years. He was a member of the investigators that had examined the data from the 2002 Dunedin sample. Di Forti examined more than 900 first-episode psychosis patients and over 1,200 community controls across 11 sites in Europe and Brazil in an observational study.[25] This is the largest and most informative epidemiologic investigation carried out to date, looking at the relationship between cannabis smoking and the new onset of psychosis. The research is notable because of its large sample size and wide range of cannabis potency at the various study locations. For example, in Amsterdam, London, and Paris, high-THC cannabis is readily available, whereas these chemovars had not yet reached Italian cities such as Palermo that participated in the study. Statistical models used by the investigators estimated that daily cannabis use was associated with an increase of just over three times the odds of developing a psychotic disorder compared with people who had never used the drug. This study excluded

individuals who met criteria for only short-lived psychotic symptoms resulting from acute intoxication, such as some of the case examples encountered in Chapters 2 and 7.

A quick statistical diversion into odds, likelihoods, and probabilities will help in understanding Di Forti's findings. Ladbrokes is a century-old betting and gambling company in the United Kingdom that is rumored to allow punters to wager on any event. Their offices will provide odds not only on the outcome of racehorses and sporting events but also political contests and world events. Epidemiologists too use the term "odds ratio" (abbreviated to OR) to quantify risk for an event occurring. Let's unpack the term a little bit. The difference between "probability," "likelihood," and "odds" is as follows. "Probability" is the percentage that something will occur; if you flip a coin repeatedly, the probability over a million coin tosses that it will come up heads is 50–50, or 0.5. Probabilities are always expressed as some number between zero and one. "Likelihood" speaks more to the probability that a certain outcome will happen. For example, theoretically in your coin-toss experiment you could come up with heads 10 times in a row, but the likelihood is low. The "odds" of an event are simply a ratio of the probability that the event will occur divided by the probability that it won't. Epidemiologists favor case-controlled designs. For example, population X lives near a toxic waste dump; population Y lives 25 miles away; is population X at increased risk of developing lung cancer? We can't really calculate the probability of disease accurately in each of the exposure groups. Therefore the relative risks cannot be pinned down precisely. But we can compute the odds of the disease in each of the two groups and then compare the two values by calculating the odds ratio (OR). Unlike probabilities, odds ratios are open-ended; if I smoke a pack of cigarettes a day for 50 years, my OR for lung cancer may be 20; if I kiss someone with an active COVID-19 infection, my OR for developing the illness may be 100. I'm merely guessing at this latter number and certainly not volunteering for any study that aims to answer this question. "Incidence risk ratio" is a related statistic. "Incidence rate" is the number of events divided by how long someone is at risk for something occurring; "incidence risk rate" puts a number on the rate of a disorder in people exposed to something divided by the rate in the unexposed individuals—it's a helpful estimate in cases where the risk is relatively low. Keeping the above definitions in mind, let's look at some of their applications as applied to studies of cannabis exposure and schizophrenia risk.

The overall population risk of developing schizophrenia is somewhere around one new case in every 100 people. The equivalent risk in individuals who smoke high-THC cannabis daily, beginning in their teens, may be two such cases. Theoretically, one of these affected individuals may be somebody who was already destined to develop the disorder (although there is no current way of knowing that for sure). The drug may have served only to nudge them in the direction of illness a little earlier. Alternatively, the second case of schizophrenia may be somebody at lower inherent genetic risk, or at slightly elevated genetic risk but with more environmental protective factors such as being raised in a loving,

stable home. Nevertheless, they are propelled down the road to the disorder as a result of cannabis use. By this logic, for cannabis-exposed individuals, the incidence risk ratio for schizophrenia is two.

So, back to Marta Di Forti. Her study determined that the OR for new-onset psychosis increased from 3.2 for daily cannabis smoking to 4.8 for daily use of high-THC cannabis types.[25] In other words, the risk for a psychotic illness increased almost 5 times in individuals who smoked cannabis with a THC content of 10% or greater every day, compared to people who never used. The odds among users of high-potency cannabis overall (adding together people who used daily and those who used less often) were 1.6 times higher. In a radio broadcast on this issue, Dr. Di Forti made the dosing analogy of high THC-content cannabis to the link between alcohol consumption and liver damage. Drinking a bottle of whiskey a day may be more toxic to your liver than 20 bottles of beer,[31] although the total amount of alcohol consumed may be equal. To clarify the status of the patients, these new-onset-psychosis individuals in her study consisted of cases whose key symptoms such as hallucinations were nontransient and sufficiently serious to have come to the attention of a psychiatrist, although not necessarily diagnosable as schizophrenia. There was no evidence that these individuals had exhibited any mental illness prior to their cannabis use, nor (unlike the Swedish study we discuss next) did they have strong family histories of schizophrenia. Their genetic status with regard to polygenic risk scores for schizophrenia is very important, but it was not measured here. (A polygenic risk score sums up all the individual risks carried by each SNP variant associated with schizophrenia across hundreds of thousands of genes to arrive at a composite genetic risk number for a particular individual.) Di Forti's study also tried to control for the effects of stimulant medications such as cocaine, as well as possible confounds from socioeconomic status and educational level.[25]

Overall, Di Forti determined that the adjusted incidence rate for psychotic disorder was related both to use of high-potency (high-THC) cannabis r=0.7 and to daily use r=0.8, and these two effects seemed independent of each other. The epidemiologists went on to calculate that if high-THC cannabis were no longer available, then 12.2% of cases of first-episode psychosis could be prevented across the 11 sites, rising to 30% of cases in London and 50% in Amsterdam. Interestingly, and in sharp contradistinction to the Dunedin study, starting to use cannabis by age 15 only slightly increased a person's OR for psychotic disorder. Furthermore, this small boost in risk was not independent from how often he or she used, or how much THC was in their cannabis.[25] Short of testing people's urine and hair for THC metabolites (which would tell us more regarding their recent historical use) or actually testing cannabis samples from each participant supply for CBD and other cannabinoids as potentially protective or risk-modifying factors, this study was carried out in an extremely rigorous fashion. The fact that it was performed in multiple cities across Europe adds to its generalizability. Because of the impossibility for ethical and practical reasons (as we discussed earlier) of conducting a random population challenge experiment, the Di Forti

observational study presents important epidemiologic evidence for links between cannabis use and psychosis risk.

Because Marta Di Forti and her team were not able to gather detailed information about the cannabis-using individuals who developed psychosis *before* they became ill, they were however unable to address one key question. That is, were these individuals likely to have developed the disorder anyway, and cannabis merely nudged them along the path to illness? Or, on the other hand, did it truly cause the illness in people who would never have developed chronic psychosis to begin with? This is an important issue to address, and it is not just a theoretically interesting but unresolvable chicken-or-egg paradox but one that is actually answerable. And indeed it has been answered.

A recent study sheds important light on this issue. Kenneth Kendler at Virginia Commonwealth University is a scholarly, much-published psychiatrist, schizophrenia researcher, and geneticist. He and his collaborators conducted a detailed study of over 7,500 individuals in Sweden, land of socialized medicine, meticulous record-keeping, and careful patient follow-up, to address this exact chicken-egg question.[32] First, they identified people who had developed a short psychotic illness that lasted for a month or more in the context of drug use. These are individuals like James in the next chapter, who developed an acute persisting psychotic state that was clearly linked to cannabis consumption. They followed all these 7,606 individuals using a carefully detailed Swedish national health registry. An average of seven years later, the investigators figured out what the subjects' current psychiatric diagnoses were. They also tracked whether these individuals were working and identified all their close and distant relatives. And by searching the countrywide health registry, the researchers determined how many of these relatives carried a diagnosis of schizophrenia.

The most important findings are as follows. The drugs that were associated with the initial relatively short-lived psychotic episodes were mostly alcohol, cannabis, and stimulants such as cocaine and amphetamine. No surprises there; all these drugs are known to increase risk for psychosis. Overall, just over 10% of the individuals with a brief psychotic episode occurring in the context of substance use went on to develop schizophrenia by the time of the seven-year follow-up. These latter were people who resembled Janet (in the next chapter), who had a chronic psychotic illness that qualified for a diagnosis of schizophrenia. This 10% figure is significantly higher than the average 1% population risk for schizophrenia. So the first key point is that experiencing the earlier brief substance-induced psychosis episode had boosted these individuals' risk for schizophrenia by 10 times. Here's where cannabis enters the picture. Those people who had converted to schizophrenia by seven years after their initial episode were more likely to have used cannabis than any of the other recreational drugs. Nearly 20% of such people went on to develop a chronic psychotic illness. On the other hand, fewer than 5% of those became psychotic after abusing alcohol. The risk for stimulant users lay somewhere in between these percentages. Outside of cannabis use, what else predicted that a given person went on to develop schizophrenia?

One factor that put individuals at risk of developing schizophrenia after their initial acute psychotic episode was being sufficiently sidelined by that first illness to have to apply for permanent disability. Also, as a group, the 7,000-plus people who started off with a diagnosis of substance-induced psychosis were much more likely than average to have family members who were substance abusers. Again, no surprises; substance use tends to run in families. But more intriguingly, they also had higher numbers of family members with a diagnosis of schizophrenia than the average person in the street. But when the 10% who converted to schizophrenia were compared to the 90% who didn't, those who had later developed the more serious illness had many more affected relatives than did the 90% who never progressed to chronic psychosis.

So what are we to make of Kendler's Swedish data? One obvious conclusion is that while substance use (especially cannabis) may be pushing people in the direction of psychosis, those who develop a permanent serious illness following use of the drug seem to have been already at risk for the disorder based on their family history of schizophrenia. So the drug likely did push them a bit further and faster along a path to illness that they were presumably already on due to their genetic risk. But cannabis most likely "does not *cause* schizophrenia [my emphasis], even among individuals who have developed psychosis as a consequence of such substance abuse." [33] That's not to say that cannabis is blameless or that we can ever know for sure based on family history who will or will not develop schizophrenia. But we can say that those who develop chronic psychosis in the context of cannabis risk are not just random individuals. At least from Kendler's data, they are people who started off life at increased genetic risk of schizophrenia by virtue of having family members with the same illness.

There are two other practical lessons to be drawn from these facts. One is that people who develop a short-lived psychotic illness that lasts a month or more related to cannabis use should quit using cannabis, because their risk for developing schizophrenia is 10 times higher than that of the general population. The other lesson is that if somebody has a family history of schizophrenia, then they are taking a calculated risk if they use cannabis, and they probably shouldn't be tempting fate.

Whole country population data add another jigsaw-puzzle piece to the cannabis-psychosis question. As the THC content of cannabis gradually rises, do rates of schizophrenia also increase? A pair of recent Danish studies [34,35] revealed that the incidence of cannabis-induced psychosis doubled from just under three per hundred thousand in 2006 to six per hundred thousand in 2016, and it had actually tripled since 1994. This increase paralleled the rise in cannabis potency. Based on Danish cannabis-use prevalence, the researchers estimated that around 1% of regular cannabis users would develop a cannabis-induced psychosis within a 10-year period. In a related study, the same group of researchers looked at around 7 million individuals and over 45,000 cases of new-onset schizophrenia. Digging into the statistics, they found that young men may be especially susceptible to effects of cannabis boosting schizophrenia risk. At a population level, assuming a

causal relationship between cannabis use and schizophrenia onset, they calculated that about one in five cases of the disorder in young men might be triggered by cannabis. Summarizing all the above information speaks to policy decisions regarding cannabis use and access in adolescence. There is accumulating evidence that regular cannabis use in adolescence, particularly for men, especially at higher THC concentrations and in those with a family history of schizophrenia, significantly boosts risk for developing schizophrenia.

Does using cannabis lower your IQ?

The trope that "dope makes you dopey" is frequently invoked, but what's the evidence for this? For example, chronically cannabis-intoxicated daily users may be portrayed as overly mellow and slow on the uptake, but do these effects vanish if users abstain from the drug for a few days or a few weeks? Or do they persist forever? University of Pennsylvania investigators reviewed almost 70 cross-sectional studies of cognitive functioning in a total of over two thousand adolescent and young-adult cannabis users.[36] They concluded that "associations between cannabis use and cognitive functioning . . . are small and may be of questionable clinical importance for most individuals. Furthermore abstinence of longer than 72 hours diminishes cognitive effects associated with cannabis use." Although this review was restricted to cross-sectional studies, because of its scope it does provide useful information. But what happens when we follow the same set of individuals across time, beginning before they ever used cannabis? Relevant evidence comes again from the Dunedin study. Madeline Meier and her coworkers looked at cannabis use in participants at ages 18, 21, 26, 32, and 38 years.[37] Neuropsychological testing was carried out at age 13, before people began using cannabis, and again at age 38. These researchers reported that people who used cannabis persistently had declines in their neurocognitive test scores over time and reported more subjective thinking problems, even after controlling for years of education. Cognitive impairment was most obvious in adolescent-onset cannabis users; and the more people had used the drug, the greater their degree of cognitive drop. This type of dose-response relationship suggests the existence of a real phenomenon. For individuals who had smoked heavily as adolescents and then quit, stopping use did not fully restore their missing IQ points back to baseline pre-drug levels. The investigators tested the participants' cognitive abilities in great detail, looking at verbal and performance IQ as well as almost 20 tests of different psychological domains. The advantage of this longitudinal study design was that each participant acted as his or her own control. Given that everybody started with a different IQ score as a child, it was straightforward to see whether people's scores went up or down over time in relationship to their cannabis use. The researchers were also able to examine dose effects, in terms of whether an individual had used cannabis at the time of one, two, three, or more of the study evaluations. What did they find? Study participants who had never used cannabis had a very slight increase in IQ over time. For users, there was a steady decrease

in IQ proportional to the number of study occasions that a person had smoked cannabis. For example, 38 people who endorsed using the drug at three or more study waves had a decline of around six IQ points. Since IQ captures general function across a large number of cognitive domains, one question is whether any specific area of ability seemed particularly affected. When Meier and her crew probed this issue, carefully adjusting for childhood IQ and the subjects' sex, all domains seemed equally impaired. The bottom line was that persistent cannabis use over 20 years was associated with cognitive decline, that longer-term use was associated with bigger IQ losses, and that the effect was restricted to adolescent-onset cannabis users.

The investigators tried to rule out alternative explanations; they calculated effects of recent use of cannabis (were their subjects stoned when being tested), persistent tobacco dependence, use of alcohol or other recreational drugs, or schizophrenia. Any or all these possibilities could impair IQ. The statistics get very complicated, but the researchers were fairly confident that cognitive effects stayed significant when adjusted for all these potential confounding variables. The Dunedin scientists wondered whether the neuropsychological impairment associated with cannabis had any effects on their subjects' everyday functioning. They checked out that possibility by asking each participant in the study to identify individuals who "knew them well." With the permission of the subjects, these informants were then contacted and asked to complete a checklist. Among other items, this queried whether the study member seemed to have shown problems with their attention and memory over the last year. Those with persistent cannabis dependence were identified by their compadres as having significantly more problems in those areas. So, case closed, you would think. Smoking dope makes you dopey. But not so fast.

Within a year of the Dunedin report, another paper was published in the same scientific journal challenging Meier's findings and suggesting that socioeconomic status might be a factor explaining both changes in IQ and likelihood of using cannabis as an adolescent.[38] To quote Rogeberg in that later publication, "This model . . . would predict reduced IQ in so far as heavy, persistent adolescent-onset cannabis use involves a culture and norms that raise the risk of dropping out of school, getting entangled with crime, and other such behaviors. . . . Because the effect in this case would be a result of culture rather than pharmacology, it would also have different policy implications." In other words, cannabis might be along for the ride statistically speaking, but it is not causal IQ-wise. Another example of correlation not equating to causation. But how could that hypothesis be tested?

The Dunedin finding was undermined using a different scientific study design. Epidemiologists: meet geneticists. Nicholas Jackson from the University of Southern California, William (Bill) Iacono from the University of Minnesota, and collaborators from Sweden and Pennsylvania examined data from two longitudinal studies of adolescent twins, numbering around 800 and 2,300 individuals respectively.[39] The twin samples studied at the University of Southern California were recruited from LA-area school districts, and those at the University of

Minnesota were drawn from two twin cohorts derived from the general population. I will not resist the temptation to allude to the Minnesota twins. Because twins mostly come from the same family backgrounds (unless separated early in life) and are very similar to each other genetically (in fact almost identically so in identical twins), they constitute the perfect controls for each other. If one twin smokes cannabis and the other doesn't, for example, then you have a nice tightly controlled mini experiment that tends to rule out confounding factors such as family background and socioeconomic status. Notionally, this is somewhat similar to the thought experiment I've referred to earlier, where half the population is chosen to be deliberately exposed to a drug and half to placebo. With epidemiologic twin studies, a researcher is able to look across the entire twin sample and summarize all the relevant effects. For the Minnesota and California samples, the researchers had measured their twins' intelligence between 9 and 12 years of age, before any involvement with cannabis, and repeated these IQ measures between ages 17 and 20 years. As in the Dunedin study, marijuana users had lower test scores relative to cannabis nonsmokers and also showed significant IQ falls over the time of the two measurements. But here's where the similarity in findings ends. Not only was there no relationship between how often people used cannabis and their change in IQ, but the cannabis-using twins showed no more IQ decline than did their cannabis-abstinent siblings, whose IQ measures also fell. How could that possibly be the case? Getting high in adolescence, as the investigators point out, "occurs within a broader delinquent context in which alcohol and other drugs are used." And when the investigators included binge drinking and other drug use in the model, the effect of marijuana use on vocabulary decline entirely disappeared. So for a start, IQ decline no longer seems to be specific to cannabis use but rather related to general substance involvement. So why, you are probably asking yourselves, would IQ also decline in the abstinent co-twins of the cannabis-using subjects? The explanation favored by Jackson, Iacono, and their colleagues was as follows. First of all, in the baseline assessment before any subject even used marijuana, future cannabis users already had significantly lower-than-average IQ subtest scores. Thus, cannabis did not lower their IQs; they were low from the get-go. This observation undermines the temporal association we discussed earlier, at least in these samples. Next, the data indicated that at least part of the relationship between cannabis use and IQ reduction was due to common underlying risk factors that accounted for both phenomena. For example, numerous studies show that being behaviorally disinhibited (such as displaying conduct disorder, delinquency, acting out, and excessive risk-taking) is a trait that predicts both substance use disorder and lower IQ. Social factors, such as coming from families that do not value education and are more lax in supervision of children, may be a factor as well. Along with that, delinquent kids are less likely to perform well academically due to their attitude to education and school absence, and they are more likely to use drugs.[39] So, went the argument: cannabis had not caused the plummeting IQs. A collection of socioeconomic and family factors had led to both.

Faced with two apparently contradictory findings from two well-conducted studies, how can this issue be resolved? One difficulty in comparing the twin study to the Dunedin sample data is that the latter looked at 38-year-old individuals who had used cannabis over a significantly longer period than had the 17- to 20-year-old twins. Perhaps prolonged exposure and the passage of time are necessary for effects to become more manifest and measurable. Or perhaps longitudinal cohort studies and twin studies are somehow inherently not comparable. But this is where our story gets even more interesting.

For those of you who might still believe that science is not exciting and lacks battles, in 2018 Madeline Meier, Avi Caspi, Louise Arseneault, and many of the original Dunedin investigators decided to look for themselves at associations between adolescent cannabis use and cognitive decline in a large sample of almost two thousand twins from the British Environmental Risk Longitudinal Twin Study.[40] In other words, they crossed the methodologic divide and adopted the other side's research design, perhaps in the hope that their scientific rivals' findings might fail to replicate. The British teens they chose to study were members of a nationally representative cohort of twins born between 1994 and 1995. Here, IQ had been measured at ages 5–12 and 18, with additional testing of executive function at the last time point. Cannabis use and dependence were assessed in the 18-year-olds. So what did they find? An effect more like that from the Dunedin study or one more closely resembling the Minnesota and California results? The results were clear. Adolescents who had used cannabis (compared to those who hadn't) had lower childhood IQs before they ever smoked the drug and also lower scores at age 18. IQ scores in those with cannabis dependence were nearly six points lower at age 12 and seven points lower at age 18 than those without such use, but scores didn't decline across that time. Cannabis users also had worse executive function overall at age 18, but crucially, as in the Minnesota study, it was no lower than their non-cannabis using co-twins. To their credit, the investigators published these findings and made no attempt to explain them away. They concluded that "short-term cannabis use in adolescence does not appear to cause IQ decline or impair executive functions, even when cannabis use reaches the level of dependence. Family background factors explain" these relationships. This result is particularly notable since the investigators identified no effect of cannabis on IQ, even when their teen subjects had reached a more serious level of drug use (dependence) than previously studied, where one would expect any negative consequences of the drug to be more apparent.

The most parsimonious explanation that helps reconcile these rather different findings is that adolescent cannabis use may not have a detectable impact on cognition unless it occurs at very high levels or is spread over many years.[41]

A rather sobering study of the consequences of adolescent cannabis use comes from an integration of data across three large longitudinal studies from Australia and New Zealand.[42] The number of participants (depending on the individual factors analyzed) varied from approximately 2,500 to around 3,800. The study looked at the maximum frequency of cannabis use before age 17 and measured

how the study subjects were faring in the community up to age 30. The outcome was dismal. There were dose-response relationships between how often the individuals had used cannabis as adolescents and unfavorable adult outcomes. These ranged from their being less likely to complete high school or to obtain a university degree. Adolescent users were also more likely to have adult cannabis dependence, to be using other illicit drugs, and to have attempted suicide. Taking a step back, the conclusions of this study must be tempered by the caveats we discussed earlier, namely Rogeberg's hypotheses about rebellious adolescent culture and the many subsequent adverse outcomes associated with an impulsive, acting-out youth.[38] Again, in other words, the argument would be that antipodean cannabis users' dismal adult outcomes were driven, along with their cannabis use, by their preexisting culture and temperaments. That view finds some support from a British epidemiologic investigation on cannabis use and IQ. This study assessed 15- and 16-year-olds from over two thousand teens participating in a longitudinal study of children and their parents.[43] After statistical adjustment, those who had smoked cannabis more than 50 times did not differ from never-users on either IQ or educational performance. Any relationship between cannabis use and either outcome pretty much evaporated when cigarette smoking was factored into the calculations. In fact, there were strong relationships between cigarette use and educational outcome that persisted even when the cannabis users were excluded from the analysis.

What's a bottom line under all these seemingly contradictory epidemiologic studies? A reasonable conclusion is that while cannabis use in teenagers may have possible detrimental effects on IQ, the results are hardly definitive and are complicated by many potentially confounding background factors. For that reason, many of the investigators in the field are awaiting the outcome of the recently begun Adolescent Brain Cognitive Development (ABCD) Study that is following eleven thousand US 10-year-olds in a very large national epidemiologic sample with serial IQ testing and brain imaging.[44] This cohort study will capture the trajectories of normal brain and IQ development beginning prior to any substance use and will start to document any longitudinal consequences.

Chapter 7

TOXICOLOGY

> The stuff I got'll bust your brains out baby, ooh, it'll make you lose your mind.
>
> ROBERT JOHNSON, "Stop Breakin' Down Blues," 1937[1]

> The basal ganglia of the brain are likewise stimulated, causing a 'welling up' of the primitive emotions. Fear, sex, aggressiveness, elation come to the surface, all colored by the imaginative processes that have been set in train by the psychic areas. These cause . . . sex delirium in acute cases and sex perversion in mild and chronic cases; aggressive outbursts; grandiose delusions.
>
> D. M. JOHNSON, *Indian Hemp: A Social Menace*, 1952[2]

> Man: It's not about how many times you fall, it's about how many times you get back up.
>
> Patrol officer: Sir, that's not how field sobriety tests work.
>
> ANONYMOUS

This chapter tries to address many questions. How potentially harmful is cannabis as a drug—and how does it rank in this respect with other drugs, from alcohol to heroin? What happens to THC once it gets into your body? How long does it stay there, and how is it metabolized and excreted? How do laboratories test for the presence of cannabis in your urine, blood, and saliva? What are the various potential ill effects of cannabis on physical and mental health? What about possible marijuana contaminants, such as pesticides or fungal spores? In the case of chemovars, how do we measure the content of different cannabis constituents? What else should be measured in the plant to standardize the cannabis that we consume? How is this information passed along to consumers? Does the concentration of THC in cannabis have anything to do with health effects? What are long-term consequences of cannabis use on the brain? While pondering these questions in the summer of 2019 during a visit to Denver to observe cannabis research, I decide to take a break in order to explore what is new in the weird and wonderful world of cannabis products. Who is using which consumables, where, how, and with what consequences? Here are a few impressions of what a legalized cannabis future might look like.

Out on Denver's "Green Mile" of cannabis-themed businesses, the dispensaries I poke my head into have myriad merchandise on offer. I'm hungry, so things that first catch my attention include fast-acting edibles incorporating encapsulated forms of THC that are rapidly absorbed from the GI tract, such as fruit-flavored candy powder with THC. Dutch Girl stroopwafels are lemon- or cinnamon-

flavored crunchy cookie sandwiches with a thin middle layer of chewy THC-enriched caramel, each containing 9 mg apiece. Other edibles include CannaCubes cherry micro lozenges and Cannavative's "indica gummiez." There are seemingly endless varieties of vaping devices for sale everywhere. Some are very high end, aimed at well-off weed consumers who want to make an impression on fellow cannaseurs. For the traditional flower user on the go who dislikes mess and is clueless when it comes to grinding and weighing, one company seems to have taken a hint from Keurig and markets flat-topped cones of 1-gram "pre-bowls" in different varieties to pop directly into your pipe.

But my wandering and gawking isn't addressing some of the scientific questions that I want to explore. Here are a few of them. Many cannabis researchers rely on subjects' self-reported measures of weed consumption. Basically, I want to know how much of what are they using and how often do they use it? People's memories are notoriously fallible for all sorts of things, including substance use. Furthermore, cannabis is a substance that notoriously interferes with short-term memory. Accurate quantity and frequency estimates are important to research in a variety of contexts. For example, let's say a researcher is trying to assess the relationship between how much cannabis people use and how anxious they feel, whether they have memory difficulties, or their risk of developing psychosis. To address those questions accurately, having an accurate metric of the amount of drug used is just as important as measuring the outcome. Sure, it's possible to take blood or hair samples and analyze them as markers of cannabis use reaching back days or months, but the process is somewhat invasive, and the lab tests are expensive. The quickest route is to just ask people to estimate how much cannabis they use. But how accurate are such self-reports? This key question can be answered empirically. One approach is as straightforward as sitting cannabis users down with some of their favorite product and asking them to estimate how much of it is in a standard unit, such as a gram or an ounce. Are they accurate or hopelessly off target? Knowing of my interest in this topic, two collegial cannabis researchers at Colorado State University have invited me to sit in on one of their measurement experiments at Denver's Cultivated Synergy meeting space.

Private clubs in Denver have official designation as private residences, so cannabis can be legally consumed inside their doors. At some such venues, vendors demo their new products and can distribute free samples, although they are not allowed to sell them there. The demos are a legal strategy to distribute "testers" and to introduce potential consumers to sample products that they may subsequently decide to purchase at their local dispensary. This arrangement is a nice compromise to deal both with Denver's public consumption law, which prohibits cannabis use in public spaces, and also with legal requirements that forbid selling weed product outside legal dispensaries. I'm about to enter one of these private clubs.

Stepping inside the door of Cultivated Synergy, one encounters a pleasant open-design meeting-and-display space with interesting art on the walls. The

interior is furnished with easily movable desks, tables, and screens that allow it to be quickly reconfigured. This is one hub of cannabis culture and identity in Denver where concentrate makers, marijuana users, and merchants of various cannabis products rub shoulders, while consumers use their own products or sample the giveaways. This space is a cannabis-related business location during the day and transforms into a private club for cannabis users at night. A speakeasy it's not. It's friendly but definitely businesslike. I show my driver's license to Cecile, the event manager, sign myself in, and get an official wristband for the evening.

Mingling with the population here I find myself amid the rich dank odor of mixed terpenes emanating from multiple sources, with people using various rigs, pipes, and vaping devices as well as the expected joints. I'm impressed by how normal and casual everything seems. People have abandoned the furtive, conspiratorial mien that was an inseparable part of cannabis use in the past. Using weed here is no different from sipping a beer at a social or a coffee at Starbucks. Although alcohol is available, few people are indulging, and nobody seems to be drinking more than a single beer throughout the evening. The clientele may be stoned, but they are calmly chatty, chilled, and friendly. Inside a typical bar at this time of the evening, people would be likely garrulous, disinhibited, loud, and a little pushy. The mood here is vastly different, and I don't see anything resembling the cannabis equivalent of being "all liquored up." Cecile tells me that in the three years that Cultivated Synergy has been open, there have been zero confrontations from guests. Having known several bar and pub owners over the years, one would never hear such a claim from one of them.

Nighttime events here include well-attended budtender appreciation evenings and "dab and dine" events, where cannabis dabs with different terpene profiles are paired with appropriate foods. Cecile tells me it's easy to recruit chefs for the dab and dines (D & Ds) because many of the local chefs are enthusiastic cannabis users. She hands me a pile of recent menus. Some of the latest D & Ds have featured such dishes as shrimp sautéed with fresh dill and drizzled with a lobster cream sauce atop toasted crostini, paired with the flavors of "Flo Live Sugar" concentrate blend, whose dominant terpene is terpinoline. According to the tasting menu, "The floral, lemongrass and pine flavors of the Flo pair well with seafood, offering a sweet and crisp experience." Similar events have also paired terps with ciders and other food varieties. Quoting from another concentrates-meets-delicacies menu, "Harambe Adhesive Honey Bucket, a distinctive cannabis flavor showing rich dark tones of umami and back-of-palate intrigue . . . is a natural companion to a dark chocolate dessert. The boudin is a perfect complement to the heft of flavors but lightness of aftertaste."

But tonight Cultivated Synergy is not about gourmet tastings. I have been invited to witness a research study by two faculty members from Colorado State University's psychology department. Brad Conner is a professor and director of addiction counseling, and his colleague and collaborator Mark Prince is an up-and-coming faculty member. They make an intuitively complementary scientific

pairing. Brad is more energized, cerebral, and detail-oriented, while Mark at first blush appears to be more of a laidback, thoughtful observer. He turns out to be a skilled schmoozer, persuader, and dealmaker who helps the science move along. Tonight they've taken over the space, together with a gaggle of their graduate and undergraduate students, to continue their research on measurement accuracy. At three separate screened-off tables, individual newly arrived marijuana users from the club are making estimates of quantities of different forms of cannabis, from dabs to flowers. Just as plate size in a restaurant can skew one's view of portion size, the psychologists are interested in how different cues affect judgments of cannabis amounts.

At one table, a student researcher is asking a volunteer to estimate 1 gram of flower and to load it into an unused glass pipe. The pipe is then weighed, and the amount of cannabis recorded, out of sight of the volunteer. At another table, the instructions are similar except that the remit is to roll a 1-gram joint. On this table there are visual cues as examples, consisting of life-sized images of various amounts of cannabis, for example flower, rolled cigarettes, and so on, along with their corresponding weights, photographed next to familiar-sized objects such as bottle caps. At the third table, the cues are pre-weighed actual chunks of bud and rolled joints in different labeled weights, providing real-world 3D examples. Brad and Mark are determining how accurate these regular cannabis users are at estimating the quantities they typically consume, whether it be dabs or flower, and whether their accuracy is helped at all by the presence of different types of cues. Because of the legalization of recreational marijuana in Colorado, many people in-state are addressing important questions regarding predictors and consequences of drug use in various populations. In past experiments similar to tonight's, the two researchers have shown that budtenders, whose jobs involve repeatedly weighing quantities of different cannabis products as accurately as possible and who are almost invariably cannabis consumers, are extremely inaccurate in estimating cannabis amounts under these research conditions. And this isn't (as you might imagine) because they arrived at the event already terminally stoned. The method used here captures volunteers at the start of the evening before they've had much of a chance to catch a buzz. In addition to participating in the weighing experiments, the volunteers are also completing interview surveys about their cannabis use. I am the proverbial fly on the wall observing what's going on, buzzing from table to table and listening in. The research subjects seem happy to participate, and one makes the comment that she has "never been so open about my weed use to anyone before."

I look for the source of cool air and see that a large fan is blowing from the balcony as the atmosphere in our space thickens palpably with exotic plant particles. People who have completed the weighing experiments hang out and begin using their own cannabis. Some in the counter area start using concentrates. Over in that corner, a Bee-Nails electronic box is heating a vaporizing coil mounted atop a compact water pipe. I wander over to observe. A friendly middle-aged businessman cleans the rig meticulously with a Q-tip before depositing a

caramel-colored sliver of concentrate the size of a sesame seed on the hot metal. To accomplish this, he is using a small, skinny metal surgical-looking spoon that would not look out of place in a nail salon or orthodontic suite. He's happy to tell me all about how this setup works and why he likes to use it. The local manufacturer's blended concentrate contains 66.15% THC and zero cannabidiol (CBD), he tells me. He dials up the device temperature to 582°F. This is sufficient to vaporize all the volatiles instantaneously but not to fry or char anything in the mixture. Before the vapor can waft away into the room, Mr. Businessman caps the cup-shaped chamber deftly with a metal cover, from whose half-dome top protrudes a nonconducting metal handle that avoids transmitting heat to the user. It calls to mind a high-tech version of a 17th-century candlesnuffer. He says that he usually prefers to set the gizmo at a lower temperature to appreciate the terpenes a bit better, but tonight is more about a quick buzz than a leisurely experience. Watch out for "lung burn" at high temperatures, he warns. A quick mental calculation tells me that the amount of THC Mr. B. is currently sucking into his lungs so efficiently from the bong is theoretically sufficient to stop a charging lion in its tracks, yet he not only fails to appear intoxicated but continues to discourse informatively on dab-related topics. This has to be an impressive illustration hypothesis of the body's capacity for THC tolerance in action. "Always check the label to figure out the THCA-to-THC ratio as well as the overall content," he continues. He runs through descriptions and ratings of different products and manufacturers faster than I can scribble things down. This brand of shatter beats that variety of crumble by a mile but is inferior to someone else's new version of budder that has a better blend of terpenes and is cheaper. Half a gram of dabs provides up to about 20 hits, he tells me, and at around 75% THC on average, that totals 375 mg of the magic molecule.

The different tools lying around serve different purposes. Some are crafted to slice and dice the product, others to scoop and dump it efficiently. One is designed to deal with syrupy concentrates, another with hard and brittle ones. "Heat this one before using, don't heat that one." Mr. B. is exhaling surprisingly large clouds to have originated in such a tiny dab. While we chat, a gaggle of dab hands forms around the rig to sample the demos and schmooze. In turn, each user selects a blob of concentrate ranging from roughly the size of a pinhead to that of a plump grain of basmati rice, nicely covering a spectrum from cautious micro-dabbers to super-tolerant gourmands. There's a fair amount of semi-intense coughing going on. Most of the dabbers are drinking lots of cool bottled water, but contrary to my expectation nobody is sweating like a horse, looking poleaxed, or forgetting how to use their limbs normally. Nobody's brain falls out. Mostly, everyone is chatting pleasantly, laughing, and generally behaving, as my mother would have put it, "like a normal person." The conversation around the dab rig ranges over a number of interesting, if random, topics. I learn that many consumers still tend to buy from street dealers, both because the price is reasonable and they know the dealer socially. Plenty of the assembled club patrons use small amounts of alcohol but generally not at the same time as using cannabis. Nobody here is a cigarette

smoker, but one person is a nicotine-vaporizer user still trying to quit. A woman in her late 20s describes a cannabis concentrate company in Arizona that features their own terpene bar. Their dispensary allows the average person to mix and match cannabis products in the way they might blend custom pipe tobacco. Down in Arizona, just as an upscale cosmetics and beauty-products store will allow you to mix your own perfumes or add your individual choice of essences to shampoos or body oils, this outfit encourages you to mix personal vaporizer cartridges to suit your mood preferences. The consumer bellies up to the custom terp bar and crafts his or her own personal blend in terms of relative percentages of THC, CBD, and other cannabinoids, and the presence and amounts of half a dozen terpenes. Want more focus and creativity? Add a dab of limonene. Wish to combat short-term memory loss? Blend in more alpha and beta pinene. Some in the little gathering find the concept appealing, while others diss it as mildly pretentious.

Meanwhile the fan is blowing effectively from the balcony, and I seem to be avoiding a contact high. A number of thoughts strike me about tonight's cannabis users. Here they are quietly enjoying a good time, but is their experience devoid of risks? How many of them will be driving home from the event, and if so to what extent is their driving ability compromised by the beer? Are any of the women here tonight pregnant? Is cannabis exposure safe for their fetuses? Are people in the crowd familiar with one or another of the recent psychosis studies, and have any of them hallucinated or become paranoid for a few days after using? Is anybody here dependent on cannabis? And just how dangerous is this stuff compared, say, to alcohol, or cocaine, heroin, or tobacco? The remainder of this chapter takes up all these questions and focuses on the potentially toxic side effects of cannabis, addressing the issues from a rather different perspective than that of an epidemiologist. These are more the sorts of questions that frontline clinicians tend to ask.

How big a concern is driving under the influence of marijuana?

Driving and cannabis is a topic with important public health and policy implications.[3] As recreational and medical cannabis are increasingly legalized, inevitably more people will use these substances, and, as a consequence, more people will be driving under the influence of marijuana. The nature of cannabis-related products is changing too, with increasing THC-to-CBD ratios, and availability of edibles and concentrates capable potentially of producing profound and long-lasting intoxication. Edibles' later-onset effects may also catch drivers by surprise. While common sense tells us that marijuana intoxication likely impacts driving ability adversely, some users deny or minimize this. "I just drive a little slower" and "I'm more relaxed when I drive stoned" are responses that I hear often from my driving research subjects. My usual response is to ask them if they would be willing passengers on an airliner where the pilot was intoxicated on cannabis.

According to the National Highway Traffic Safety Administration, drugged

driving is on the rise. While the number of annual fatal vehicle crashes in the United States has trended down in recent years, as has the number of alcohol-involved deaths (thanks to police being more serious about enforcing DWI laws), the number of driver fatalities involving positive drug tests has increased. The overall death totals began falling around 2006 from about 36,000 to about 30,000, but the proportion of fatal motor-vehicle accidents involving drugged driving has risen from about 5% to about 20%. Numbers are not directly comparable, however; the number of individuals tested for drugged driving and the nature and sophistication of the testing used has changed significantly over time. Also, the presence of certain drugs on postmortem testing does not necessarily imply that the individual was intoxicated at the time of death (for reasons that we will discuss later). This relationship varies for different drugs. A 2016 meta-analysis that pooled together data from multiple studies to total almost a quarter of a million individuals concluded that cannabis-intoxicated driving constituted a low-to-moderate-magnitude risk, with the odds (recall odds from Chapter 6) of being involved in an accident increasing about 1.36 times compared to driving sober—a relatively minor increase. To put things in proportion, the odds of being involved in an accident with a blood alcohol concentration of 0.10 is somewhere around 20 times greater than driving sober, and that of driving very high on amphetamines about 55 times. The summary of the literature shows that compared to the sober state, marijuana-intoxicated drivers vary their driving speed more; have slower reflexes, causing them to take a little longer to brake; begin driving a tad later when a light turns green; tend to weave a little bit more; and are somewhat slower in avoiding other vehicles, so they're more likely to collide with them. But even such small-scale differences are important if it's your kid who is out on their bicycle at the same time as a stoned driver. The weight of evidence from many types of studies—epidemiologic, testing chronic marijuana smokers, conducting laboratory studies of consequences of acute dosing—strongly support that marijuana use causes detectable deleterious effects both on driving and cognitive test performance. When I use the term "detectable," I'm referring to what's measurable in a research lab. But is cannabis-related driving impairment detectable at the roadside? This brings us into territory of interest to law-enforcement authorities. Exactly how useful are our roadside tests in detecting recent cannabis use and consequent driving impairment? When I mention "recent use" and "driving impairment," we should not automatically assume those terms are equivalent. What people used, when they used it, and the type of driving they are engaged in all have some bearing on the issue of driving impairment.

When I first became involved seriously in this research field, I was surprised by how many key questions were only partially answered or not answered at all. Some of these numerous issues include the following. What cognitive and behavioral aspects of simulated motor-vehicle driving are impaired acutely by cannabis use? What are the most sensitive cognitive, motor, and biosensor tests to detect these impairments, and how feasible is it to get them out of the research laboratory for purposes of roadside administration? How relevant are these kinds

of tests to driver performance and safety in the real world? (For example, a test might be very sensitive to recent cannabis use but completely unrelated to driving impairment.) Once someone is impaired by an acute dose of cannabis, how long does it take for their vehicle-driving performance to return to its sober baseline? How accurate are cannabis-intoxicated drivers in estimating their own degree of impairment? What's the relationship of cannabis-caused driving impairment to the levels of THC and its major metabolites in blood or saliva? Are any of these measures related to brain activation patterns measured in a functional MRI or by an EEG device? And what's the best naturalistic test environment to answer these questions?

None of the experts seem to know what the time course of THC-related driving impairment is. If you smoke half a gram of 25% THC premium weed at 9 a.m., when are you safe to drive? Because impairment on cognitive tests cannot be assumed to be the same as actual driving impairment, it's important to validate any candidate test procedures against actual or simulated driving. The relationship between alcohol-related driving impairment when combined with cannabis impairment is also obscure. Consider this: if you're below the legal alcohol limit after drinking a beer or two and then smoke a joint, how impaired are you? Are the combined effects determined by simply adding the separate intoxication effects together, or does driving impairment somehow multiply so that the combination is much worse? Finally, no one seems entirely sure what the specificity of impairment patterns caused by THC is compared to those due to opioids or Valium-like drugs. If the police pull you over for impaired driving, and you test negative for alcohol, can they assume you're stoned, or might you be equally likely impaired by Xanax?

Cannabis is complex. Not only is there cannabinoid variation from one chemovar to another, but the over four hundred compounds in the cannabis plant produce a massive number of possible intoxicating combinations. In addition, cannabis products from edibles to dabs vary in their THC percentages, choice of potential administration methods, and absorption characteristics. Some chemovars are advertised as sedating, others as wake-me-ups. Does use of these different products elicit equivalent impairment of driving ability?

It is important to understand why the above questions remain unanswered, so let's review a few of the complexities. There are not very many well-controlled studies of cannabis-impaired driving. Also, cannabis impairment is significantly more complex to study than alcohol impairment when it comes to driving. Let me explain. With alcohol, there are very straightforward proportionate relationships between how much someone has had to drink, the levels of detectable alcohol in blood or breath, and driving impairment. For cannabis, there is no clear connection between how much drug someone has used, the resulting concentrations of THC and its metabolites in breath, blood, or saliva, or between these concentrations and actual driving impairment. We will explore the underlying reasons for why these circumstances are so different for alcohol versus cannabis a little later. But part of the explanation lies in the complex pharmacokinetics of THC compared to those

of alcohol. Because THC and its metabolites tend to hang around in the body long after use, it's unclear how to interpret body-fluid sampling after fatal and nonfatal motor-vehicle accidents. Also, rates of such accidents are subject to a skewed, agenda-driven motor-vehicle administration reporting in relationship to marijuana legalization. Nobody these days argues that drunk driving is a bad thing. But driving stoned is a disputed topic. The pro-cannabis-legalization side will tend to play down apparent increased accident rates following cannabis legalization. Conversely, it's in the interests of the anti-legalization side to exaggerate such numbers. Unlike alcohol, where there is a set of well-established, evidence-supported, agreed-on roadside sobriety-testing paradigms, not only are these procedures not appropriate for testing cannabis-impaired drivers, but nobody is entirely sure what the best tests for stoned drivers actually should be. Yet another problem is that there is a lack of sober baseline testing on presumptively impaired drivers. Maybe they were awful drivers when sober.

Let's contrast alcohol DWI to the situation with cannabis in a bit more detail. Alcohol's story is straightforward. As we all know, it is extremely soluble in water (hence cocktails), and most of our bodies consist of water. So an alcohol dose fairly quickly and readily diffuses throughout all your tissues pretty much equally. Hence the concentrations of alcohol in your brain, your blood, and your breath are very similar to one another and also directly related to how much you drank. If you take a swig of alcohol, and I wish to plot your blood or breath alcohol concentration (usually abbreviated to BAC) over time, I need to know only three things. These are how much alcohol you drank, your sex, and your body weight. With those three facts, I can be extremely accurate in predicting how high your peak BAC will be and how slowly it will fall to zero. If I know how much food was in your stomach when you took the drink, I can be even more accurate. In addition, your BAC is very tightly and directly tied to your motor-vehicle crash risk. The higher your BAC, the worse your impairment.

None of these things is true for cannabis. THC is fat soluble not water soluble. So rather than floating around your body in an equally distributed manner, there's a big initial THC peak in your blood that maxes out about 4 minutes after smoking. This rapidly diminishes minute by minute as the chemical is absorbed into body fat. Since there is lots of fat in all our brains covering the axons of neurons, the brain is one of those places that enjoys a high concentration of THC. Peak buzz usually occurs at around 15 to 20 minutes after smoking or vaping. Once that initial THC spike quickly plummets to very low levels, the drug and its metabolites persist in the body for very long periods of time, gradually leaching out of your fat stores. If you're a heavy cannabis smoker and then quit, those chemicals may still be detectable in your blood and urine two weeks or more after you last used. That's a major problem for law enforcement. There is no easy way to tell if a low level of THC or its metabolites in your blood or saliva represents the fact that you smoked a joint 20 minutes ago and your driving is currently impaired, or that you last used 10 days ago and you have long been at your behavioral baseline. Unlike alcohol, THC has no smooth decrease in its blood

levels; just that quick spike followed by a gradual decrease from a lowish level. To make things even more complicated, there is no clear relationship between those blood levels and your driving impairment because of THC's fat solubility. What's going on in your fatty brain is in no way reflective of levels in your watery blood or saliva. Essentially those blood measures are uninformative. Not only that, but driving-impairment-related behaviors due to cannabis are not straightforwardly related to dose. Remember the biphasic relationships for anxiety and THC dose, where low doses were calming but higher doses had the opposite effect? There are similar complex dose relationships for your heart rate, how much you feel the drug's effect subjectively, and perhaps some complex behaviors related to driving. The whole issue of cannabinoids' fat solubility makes blood testing hard to interpret. As people in the driving research world like to say "There is no BAC for THC." If alcohol behaved like THC, imagine you were drinking in a bar 10 days ago and had six beers but haven't had a drop of alcohol since. The police pull you over stone-cold sober at a routine roadside stop, and your BAC is still positive, so they arrest you today for traces of the beer you consumed a week and a half ago. If that seems bizarre and unfair, it's precisely the situation with cannabis. Based on drug level, the police have no way currently of distinguishing between someone who used the drug recently and is driving impaired, or who used days ago and is completely sober. The same problem applies to postmortem blood samples taken from drivers killed in motor-vehicle accidents. A positive sample does not equate to the person being incapacitated by cannabis at the time of the fatal crash. And this is something that is generally ignored by opponents of liberalizing marijuana legislation when they cite driving-related consequences of legalization based on such blood-level data. To help address this technology gap, various companies are working on a "cannabis breathalyzer" that purports to measure concentrations of one or more THC metabolites that disappear from breath a couple of hours after somebody smoked cannabis. Theoretically that instrument might be a useful guide for live drivers and a way of distinguishing between relevant recent and irrelevant distant use. But there are considerable practical problems in devising such a breathalyzer. As we've seen, soon after swallowing a couple of alcoholic drinks, your breath is teeming with millions of alcohol molecules that are pretty easy to detect on a relatively straightforward roadside screening device. In comparison, the number of relevant THC metabolite molecules in breath is minuscule, requiring a fairly sophisticated and highly sensitive detector.

Ultimately, THC, CBD, and their metabolites such as 11-nor-9-carboxy-THC (THCCOOH) make their way to hair follicles and thereby into your hair. Here, they can be detected (albeit somewhat expensively) by laboratory testing. You can cut a hair sample into segments, and since people's hair grows at a relatively uniform rate, a specialist laboratory can analyze chemical concentrations up from the root toward the tip to detect who smoked what and when. Hair analysis is a reasonable means to confirm long-term abstinence or, perhaps in Rastafarians (who do not cut their dreadlocks), a method to examine very long-term cannabis use, but obviously it is completely uninformative in people who shave their

heads.[4]

How do current procedures for driving under the influence of drugs (DUID) play out? In general, a law-enforcement officer pulls over your vehicle either for "probable cause" if, for example, you are weaving when driving, or perhaps randomly at a police checkpoint. The officer asks you to exit your vehicle and then administers roadside tests for impairment. Most such tests are based on established procedures for alcohol intoxication. Unfortunately, these screens are in all likelihood not relevant in detecting cannabis intoxication. If you perform abnormally on roadside screening (for example, not being able to walk a straight line), you are generally asked to blow into a breathalyzer in order to test your BAC. If that reading is normal, then the police may decide to have your blood drawn for drug testing at a nearby facility. The average time between law enforcement making that decision and the needle entering your vein for the sample is 90 minutes. Recall that the blood THC peak occurred 4 minutes after you took that last toke. If THC shows up in your blood sample, laws in 13 states prohibit driving with any amount of the substance detectable in plasma. But we've already seen that THC can hang around in your blood for a couple of weeks after you last smoked, so the situation is exactly parallel to our example earlier of police charging you with a DUID 10 days after your last drink. A handful of states specify a legal THC cutoff level above which driving is illegal. In Colorado, Montana, and Washington, this value is 5 ng/mL of blood; in Nevada and Ohio, the value is 2 ng. There is no scientific basis for these decisions. The remainder of US states prohibits driving while "incapacitated by" or "under the influence of" marijuana. These are slightly different legal standards, but both boil down to a somewhat vague prohibition on driving while high. Thus there is considerable and confusing variability among state DUID laws for cannabis.

Some jurisdictions employ drug recognition experts (DREs). These are police officers trained in the standard protocols of the US Department of Transportation, the National Highway Traffic Safety Administration (NHTSA), and the Drug Evaluation and Classification Program (DECP). Such individuals are certified to conduct examinations on drug-impaired drivers, usually at precincts or jails. The process involves a multistep standardized procedure that combines data of several kinds. These are medical (for example, pulse rate, bloodshot eyes), psychophysical (for example, subject sways when standing on one leg), and observational (what the DRE sees when interviewing the subject).[5] In my experience and that of many other researchers, the problem with DREs is that there is significant variability in performance from one of these evaluators to another when it comes to accurately identifying cannabis-intoxicated drivers. Since it's not yet clear to anybody what are the most reliable roadside field tests for identifying cannabis-impaired motor-vehicle drivers, under properly controlled conditions, the DREs perform about as well as the rest of us, which is only moderately. On the other hand, they do consistently well in ID'ing drunk drivers.

If the current relationship between cannabis intoxication and impaired motor-vehicle driving is obscure (which it is), then the obvious approach to establish

facts is to test drive individuals who are acutely stoned. It's neither legal nor ethical for scientists to get someone high and then have them drive in traffic on a major highway. But if you want to measure validly how impaired somebody's driving is, you really do want to test them under realistic circumstances. This is where driving simulation enters the picture. Driving simulation is the gold standard for identifying and quantifying relevant impairment. It provides a controlled, safe environment that translates ideally into real-world driving. You can easily mimic scenarios that are unethical or impractical to test in real life, such as a puppy suddenly running into the road. With a skilled programmer, you can easily manipulate the environment, including the behavior of other vehicles, whether it's day or night, or numerous different weather conditions. To avoid your research subjects learning a particular scenario after they've run through it a couple of times, you merely program a series of variations into the driving sequence. This raises the critical issue of validation. Let's say that an investigator has designed some supposedly state-of-the-art simulated driving hardware and software. How will he or she know whether actual drivers on a real road drive in a manner that's comparable to the way they perform on this experimental setup? Fortunately there is a way to answer that question.

Virginia Tech's Smart Road is a 2.5-mile-long limited-access highway located in Blacksburg, VA, that mimics an interstate and is used for advanced vehicle testing. Part of it is connected to a public road. The Smart Road is used by Virginia Tech's Transportation Institute for testing autonomous vehicles and experimental road surfaces, and it boasts a movie-set-like array of portable features, including reconfigurable buildings, alleyways, and intersections, and removable line markings. Looming over the whole enterprise is something that looks like an airport control tower from which everything can be observed and managed. For example, some of the permanent "light poles" contain water sources that can make it realistically "rain" or even "snow." Buried beneath the tarmac are hundreds of sensors that communicate with computer equipment stored in the trunks of numerous experimental test vehicles. The vehicles themselves are outfitted with dual-control devices like those in learner-driver cars, as well as cameras to monitor eye movements. The dual-control feature allows one of the experienced Blacksburg driving scientists to take over the wheel or pedals at short notice if the driver's performance becomes worrisome.

More than 25 years ago, I organized a scientific expedition down to Blacksburg and had a series of volunteers consume alcohol (sufficient to push them over the legal BAC limit) and placebo at different times. Our subjects then both drove an actual Tech Institute vehicle on the Smart Road and separately navigated a computer-based realistic mockup of the Smart Road on a driving simulator. We were able to show pretty convincingly that the inebriated volunteers made the same sorts of errors (exceeding the speed limit, speeding up around curves, weaving) on the simulated road as they did on the "real" highway. This procedure validated the driving simulation paradigm.[6]

If Virginia Tech has the coolest real vehicle test environment, then the best

driving-simulation equipment is the National Advanced Driving Simulator (NADS) located in Coralville, Iowa. Until recently it was the largest ground-vehicle driving simulator in the world. NHTSA put millions of dollars into developing the NADS (the developers obviously didn't give much thought to the acronym), which is truly impressive to behold—nerd paradise in fact. The simulator itself is a large dome that looks like a scaled-up white NASA lunar probe or an extraterrestrial vehicle about to land in Area 51. It is sufficiently large to have an entire vehicle body lowered into it. When I use the term "vehicle," this can be anything from a standard-sized sedan to an Abrams tank. The dome is perched on stubby legs that are attached to a motorized platform. In turn, the platform rides on rails that allow the dome to rotate nearly 360 degrees and to accelerate for 60 feet. Inside the dome, one can project a realistic virtual-reality highway or indeed any desired terrain. This combination of features makes anyone who's "driving" a car inside the dome (and I can attest to this) feel exactly as if they are driving a real car on a real road. All the sensory cues that are missing from most driving simulators are present here. When I drove an actual car on an authentic road soon after being inside the NADS dome, the genuine experience possessed a slight aura of unreality, as if reality wasn't quite sufficient.

Marilyn Huestis, a doyenne among cannabis toxicology researchers, ran a series of cannabis-intoxicated driving experiments, testing smallish numbers of cannabis- or placebo-dosed subjects with and without alcohol on the NADS. She was able to document that stoned drivers showed detectable weaving, even at fairly modest doses of the drug, and that volunteers using both alcohol and cannabis made a greater number of errors.[7–9] The next step for these sorts of experiments is to show more definitively how these types of errors relate to on-road driving performance.

One of my lab's contributions to the field of driving under the influence of marijuana is to try to understand what's going on at both a brain and a behavioral level in cannabis-intoxicated driving. Our experiments involve cannabis-using volunteers (both men and women to examine sex differences) who get high either regularly (almost daily) or occasionally (about once a month). Our volunteers consume either high- or low-THC cannabis or placebo provided by the National Institute on Drug Abuse (NIDA) and grown at their official supply site in Mississippi. Subjects visit the laboratory on three separate days, a week apart, to receive one of their three doses. (Parenthetically, NIDA likes to emphasize that their name is the National Institute *on* Drug Abuse, not the National Institute *of* Drug Abuse, the latter of which conjures up a hopelessly inebriated group of government scientists avidly consuming large quantities of illicit substances. Since NIDA generously funds much of my research, I will definitely venture no further in poking gentle fun at them.)

Back to our volunteers. First, they consume whatever dose they are receiving on a particular day (and everything is double-blind and randomized, so neither we nor they have any idea what that is) via a desktop vaporizer. Next, they rotate through a series of simulated drives inside the MRI scanner so we can examine

their brain activity. After that, they drive on a regular driving simulator outside the scanner, participate in different varieties of cognitive tests, and provide us with regular samples of blood and saliva for laboratory testing for THC and its metabolites. All these procedures are repeated multiple times throughout the seven-hour study day. Thus we can tell when the drug is exerting its maximal impairing effects, as well as when these wear off. The simulated driving experience in the MRI scanner involves a series of fairly realistic simulations measuring different traffic patterns of varying complexity. These driver challenges may be very simple (driving in a straight line while simulated wind gusts occasionally buffet your vehicle) or quite complex (safely passing a stalled vehicle in your lane while waiting for a gap in busy oncoming traffic). The steering wheel and gas and brake pedals are all realistic and conceptually familiar to anyone who's ever played a high-end driving video game, except that nothing contains any ferromagnetic material, so it is safe to use in the MRI scanner. The experience resembles driving, except that you are flat on your back. When one of our participants is involved in a virtual accident with another vehicle, an obvious question is what were they looking at when the crash occurred? For example, were they actually peering straight at the other vehicle but just not reacting in time to avoid the collision? Or were they instead distractedly staring at the virtual sky (such pretty virtual clouds) and not even noticing that they were about to hit another car? To parse these different possibilities, we use an infrared eye tracker so that we can see precisely what our subjects are watching at any given time.

Our research also asks other questions. For example, what is the optimal design needed for roadside testing to be effective and accurate in identifying cannabis-intoxicated impaired drivers? This information could be used to design a so-called field sobriety test administered at the roadside by law-enforcement personnel. The information could also be compared to a suitably specific and accurate assay of THC or one of its metabolites in a body fluid to see if there's any relationship between test performance and blood values.

What do forensic toxicologists dream about? The object of their desire is a really accurate and sensitive blood, urine, or saliva test that indicates specifically only recent cannabis use and correlates with driving impairment. Such a test result would identify accurately someone who had got high within the last couple of hours and didn't yield false positive results that incorrectly imply very recent use but are instead due to indulgence many days prior. The toxicologists would like their assay to indicate only recent cannabis use, whether or not the test subject generally uses cannabis five times a day or only once a month. They would add to their wish list that the test was also positive for a few hours after use of edibles and could distinguish between somebody who'd actually used cannabis personally rather than inhaled secondhand smoke. For example, the test should be negative if his or her friends were toking up in a car while the testee was driving, but he or she hadn't indulged personally. Finally, their dream assay should be capable of being processed rapidly, say within 24 hours or even better, at the roadside, and not be wildly expensive. Slower, more expensive drug tests might be fine for

screening Olympic athletes (where half of all positive drug tests are for cannabis) but are not feasible for routine roadside testing.

In their search for informative cannabis tests, toxicologists perform interesting experiments. For example, they have volunteers smoke joints, inhale from vaporizers, or consume edibles, and then they harvest their subjects' plasma and urine samples over the ensuing minutes, hours, and days.[10–12] These sorts of scientific efforts have yielded valuable information but nothing quite yet that meets criteria for their dream assay. This is what the breathalyzer companies want their devices to provide. Various metabolites and breakdown products of THC in blood, urine, and saliva (what researchers refer to as "oral fluid") are all potential flags of recent cannabis use. While a number of these test measures are somewhat useful, none yet has demonstrated the characteristics needed for quick identification of cannabis-impaired drivers.

If performance on the standard roadside sobriety tests for alcohol—such as walking a straight line heel-to-toe while reciting the months of the year backward or accurately touching your finger to your nose with your eyes closed—are not especially sensitive to cannabis effects (and they are not), then are there equivalent areas of impairment that would be appropriate for detecting acutely cannabis-impaired drivers? Many research groups, including my own, are working on this problem. One test candidate still being assessed in my laboratory (in collaboration with Colorado State University) includes using the accelerometer that's buried inside your iPhone. This is the technology that detects when you flip the device from horizontal to vertical and ensures the display remains upright. Since the device reads out several hundred times per second, it could theoretically pick up a characteristic signature body sway due to acute cannabis intoxication. Another technology is a simple portable EEG device that transmits information about your brain to a handheld laptop via Bluetooth. It takes less than a minute for someone to plop the EEG cap on your head and begin recording, so it's feasible to use at the roadside. Other technologies being explored include measuring the eye's response to flashes of light, and assessing a person's ability to interpret rapidly whirling or flashing patterns or to perform accurately on PC-based games and puzzles. All these approaches have potential drawbacks of one sort or another. For example, if you are trying to assess cognitive abilities, does the test still work at the side of a noisy highway at night with many potential background distractions? Does the EEG device work on somebody with hair extensions or dreadlocks? Does your eye respond to flashes of light differently if you have had cataract surgery? So right now, the field of developing straightforward roadside sobriety tests for stoned drivers has attracted widespread interest but has yet to come up with the killer app.

Another wrinkle in the DUID area is the fact that a fairly solid proportion of individuals who use cannabis do so in the context of alcohol consumption. We saw this use pattern among our 2,000-person college-student study (discussed later in this chapter). We also noted previously that some of the Colorado social-club attendees consumed small amounts of beer with their cannabis. Many surveys bear out the same mix-and-match tendency of concomitant use. I mentioned a little

earlier that how the intoxication effects of the two drugs add up when they are consumed together is not well understood. These types of drug-drug interactions can be complicated. For example, the metabolism of cocaine users who concomitantly drink alcohol brews up a combined compound called "cocaethylene" that both prolongs and amplifies cocaine's intoxicating effects (and toxicity) severalfold. Evidence to date suggests that alcohol may multiply cannabis's relatively mild deleterious effects on automobile driving,[7] although other studies suggest few to no interactions between the substances.[13,14] The critical experiments, parsing these effects by exploring a wide range of doses of both drugs alone and in combination, have yet to be carried out. As a result, as with many other aspects of cannabis-impaired driving, there are more questions than answers.

Delirium and psychosis

Let's switch gears. With the recent legalization in many US states of medicinal and recreational cannabis, concerns have emerged about cannabis as a risk factor for psychosis. The numbers of cases involved are not trivial; in 2017, 567 people were treated at Vancouver-area hospitals for cannabis overdoses or related mental-health issues.[15] Even if the percentage of people affected is low (which is probably the case), as more and more people find cannabis products easily available due to legalization, then the number of cases is bound to rise. But to put things in perspective, around 5 people in British Columbia actually die every day from direct or indirect alcohol effects.[16] In the prior chapter, we looked at psychosis (mainly schizophrenia) from an epidemiological-risk point of view. Here, let's dive into the clinical aspects of several different cannabis-related psychotic states.

As reviewed by Wilkinson,[17] and others, four distinct psychosis-related syndromes can be provoked by acute or chronic cannabis use. This fact alone complicates the broad statement that "cannabis causes schizophrenia." I will describe examples of each of these syndromes further, using case examples so that readers can have an idea of what typical presentations look like. Cannabis intoxication, including recreational use of synthetic cannabinoids such as "K2," can provoke both an acute (hours-long) psychosis with prominent positive symptoms (such as hallucinations or delusional beliefs) and an acute delirium. The latter is characterized by features of disorientation, waxing and waning levels of alertness (sleepy one minute, alert the next), and short-lived cognitive problems. Cannabis can also trigger an acute psychotic state lasting days to weeks beyond the acute intoxication period (subjects whom Kenneth Kendler ID'd in the first wave of his Swedish sample).[18] And finally, the drug is associated with risk for a chronic psychosis resembling schizophrenia that is not linked to recent cannabis exposure. This last group includes those Scandinavian subjects that Kendler studied in his follow-up work and Marta Di Forti identified in European cities.[19] We have already reviewed that most new cases of schizophrenia are not linked to cannabis consumption and that cannabis exposure alone is neither necessary nor

sufficient to cause a persistent psychotic disorder (although it may be a significant environmental risk factor for some individuals).

Delirium

Let's begin with delirium. The *New York Times* editorial writer Maureen Dowd wrote of her ordeal with too high a dose of cannabis edibles in that newspaper.[20] Her experience with nibbling on an edible, figuring out the absence of an effect meant that she needed to eat more, and then doing so led to a hallucinatory state that lasted eight hours. She describes "panting and [feeling] paranoid," unsure of where she was, and finally convinced that she had died.

Ah, delirium. You've no idea what time it is or how you got here, wherever here actually is, which seems distinctly open to question. It's very difficult to think straight. Time extrudes like cookie dough, and the stitching on your coverlet has transformed itself into a swarm of angry spiders. Subjectively, delirium is often confusing and frightening. As one cannabis deliriant related, "I didn't know my name or who I was or where I was or what it even means to be human and have a body and a brain. I didn't understand time or space, life or death. It was very metaphysical." [15]

Objectively, delirium is brain state identified by a combination of symptoms that can occur acutely whenever our brain is compromised from a huge variety of factors originating from outside the brain itself. Candidates include drug intoxication (for example, from cannabis or synthetic cannabinoids), drug withdrawal (for example, from alcohol or Valium-like drugs, which can cause the d.t.'s, short for "delirium tremens"), infections, liver failure, malnutrition, and sensory deprivation (like being in an ICU). Individuals with immature brains (such as children with fever) or aging brains (elderly individuals with dementia) are particularly vulnerable to delirium, sometimes known as "sundowning" in older people with Alzheimer's disease. Objectively, delirious individuals become inattentive, drowsy, cognitively impaired, and disoriented; they also hallucinate (often visually), experience delusions (often paranoid), and have disturbed sleep-wake cycles and disorganized language. A psychiatrist colleague of mine loves to relate the story of how he was called to consult on an elderly delirious patient on a medical ward who was referred by his internal-medicine specialist in the following manner. "You have to see my patient immediately. He's a man in his 70s who has acute heart failure. He was rational when I admitted him two hours ago. Now he's totally out of his tree. He thinks he is at work in the fire department and is trying to operate some kind of pumping equipment that actually isn't there. He keeps trying to get out of bed. His speech makes no sense; it sounds like he's quoting from James Joyce's *Finnegans Wake*. He can't think straight or talk right, and he won't listen to reason. What's going on?"

Delirious patients are located at any given time somewhere on a continuum between being wide awake, straightened up, and flying right on one extreme to being in a semicoma on the other. Their clinical course frequently waxes and

wanes, wandering along this continuum of consciousness over the course of hours like a drunken sailor. On an EEG, their brain waves are grossly disturbed, usually extremely slowed down and scrambled. Their short-term memory and attention are disrupted, and they are commonly drowsy. The syndrome generally rolls in like a storm front fairly rapidly, typically over hours but occasionally over the course of a few days. Focusing specifically on delirium due to cannabis, I can say that what happened to me on my 20th birthday as described in the introduction to this book and what happened to Maureen Dowd in her hellish Denver hotel room are pretty much textbook-typical examples of this diagnosis.

How does cannabis delirium come about? Let's look at a few specifics of my own case as described in the introduction. The THC in hash mostly exists in the acidic form (THC-A) and must be decarboxylated by heating it to exert any psychoactive effects. If one were to eat a bunch of raw buds, no high would ensue. So my gently warming the hashish with a quarter bar of butter in a cheap slightly battered saucepan accomplished that. Because THC is extremely fat soluble, dissolving it in butter efficiently prepared it to be absorbed from my gut. So, what went wrong for me, Maureen Dowd, and large numbers of edibles consumers every year? Since my episode devolved into a seeming interstellar misadventure, a suitable inquiry might be likened to the scientific commission convened to uncover the cause of the space shuttle *Challenger* disaster. To misquote slightly Richard Feynman's conclusion in that commission's report, "reality must take precedence over folklore, for nature cannot be fooled." [21] What was underlying reality here? Some back-of-the-envelope calculations reveal that if we assume the THC content in the 2.5 g (or 2,500 mg) of my high-quality Lebanese hash was around 15% (it was high quality), then there were 375 total mg of THC in my mini birthday cake. A typical oral dose in edibles such as a cannabis gummy bear or one square of a cannabis chocolate bar is 5 to 15 mg of THC. For a newbie, that's usually more than a sufficient quantity for a nice mellow buzz. In an entire large gourmet cannabis chocolate bar, you might find 20 of those 5 mg squares, yielding a total of 100 mg of THC. So conservatively, I had consumed 25 times the appropriate dose, or nearly four entire chocolate bars' worth. A rough equivalent would be aiming to drink a single beer and instead consuming an entire case of 24 bottles in one sitting. Or meaning to order one espresso at Starbucks but instead chugging down an entire full-to-the-brim Venti cup of pure espresso, followed by another two double shots as a chaser. In short, too much of a good thing.

Another mistake of mine was to forget that eating cannabis is a very different beast from smoking it. For a start, timing of the drug's effect differs completely. Smoking marijuana gives you an almost immediate buzz (lung to blood is an extremely fast and efficient absorption method) that has pretty much dissipated a few hours later. With edibles, nothing much happens for around 40 minutes, but once the experience starts, it can last four to six hours or more, ideal for long movies and for concerts. Not knowing the appropriate dose or the typical onset time for edibles is a common rookie mistake, and "overdose by impatience" is exactly the resulting trap that both Maureen Dowd and I fell into. Never assume

that, because nothing has happened half an hour after sampling an edible, you underdosed and therefore need to ingest a lot more. What's the science behind the need to hurry up and wait? When THC is swallowed, it's absorbed from the gut (which takes a while) and then goes to the liver, an organ designed by evolution to break down any chemicals and toxins that get into the body into simple harmless compounds that can be efficiently excreted. The first thing the liver does to metabolize delta-9 THC (and again this takes more time) is convert it into a chemical called "11-hydroxy delta-9 THC." The latter does not exist in the cannabis plant. Once manufactured in the liver, the 11-hydroxy circulates back into the blood, through which it enters the brain, even more efficiently than regular delta-9, so that it's a highly businesslike and effective chemical with which to get wasted. Some cells in the gut are also capable of metabolizing THC to 11-hydroxy and send it on to the liver. (By contrast, the blood levels of 11-hydroxy after smoking are pretty minimal, so it's mainly the delta-9 that's getting us buzzed from smoking.) This process of absorption and metabolism takes about an hour, which is why there is no immediate high from using edibles. The continuing cycle of absorption, recirculation of cannabinoid compounds, and their re-metabolism in the liver and further recirculation accounts for some of the ebb and flow of THC and its metabolic offspring in the blood, as well as the waves of intoxication that are typically pronounced following edible ingestion.

Back in 1970, the year of my resinous birthday cake, Louis Lemberger and his collaborators, the famed NIH scientists Julius Axelrod and Irv Kopin, took a batch of delta-9 THC,[22] labeled it with a small, safe amount of radioactive tracer, and injected it into human volunteers. They showed that the drug hung around in the blood for more than three days. Its metabolites began to appear in plasma within 10 minutes after the injection, where they took up residence, swirling through the bloodstream along with the parent compound. Delta-9 THC was ultimately completely metabolized to 11-hydroxy and other compounds, with the radioactive metabolites continuing to be excreted in urine and poop for more than a week. A couple of years later, Lemberger had the bright idea of administering 11-hydroxy directly to human volunteers intravenously and, in a separate experiment, comparing it directly to the same dose of intravenous THC.[23,24] In these two later experiments, volunteers, blinded to what substance they were receiving, reported that the 11-hydroxy compound got them to their peak high more quickly (in about 4 minutes) than did THC (about 15 minutes) and that they were significantly more buzzed when they got there. So the bottom line of all this examining THC metabolism is that edibles take longer to get you stoned because the THC has to be absorbed and metabolized to have its effect via that route. But once the intoxication starts, partly because of the conversion to 11-hydroxy, gram for gram the average person is going to get more intoxicated and for a much longer time than if they smoked flower or hash.

My third birthday-related mistake was what social scientists like to call "expectation bias." Given my prior experience with cannabis, I was prepared for the magic birthday cake to float me away gently into a peaceful little bower, where

colors shimmered softly, musical waves danced beautifully, and happy clouds floated peaceably by. Unicorns frolicking sedately might've been a nice extra. Being blasted at the speed of light into a seeming perpetual abyss of delirium was definitely not part of the game plan. It had never occurred to me that such a possibility might crop up, so when it arrived in the blink of an eye, there was no psychological plan B.

Enmeshed with these events is yet more science. Smoking or vaping cannabis is a faster way to get high than using edibles because the heat quickly decarboxylates the THC and other compounds. Sucking the resulting smoke or vapor into your lungs results in immediate absorption from lung capillaries and quick circulation in the blood straight to your brain. Smoking is not terribly efficient because up to half of what you're inhaling from a joint, for example, may just float away into the surrounding air and never make it into your lungs. But you can straightforwardly titrate your dose in real time because of the rapid onset of drug effects. If your high starts to feel a little excessive, you can just quit puffing. But once the edible enters your gullet, the horse has figuratively left the barn, even if the effects don't show up for another hour. If it turns out that you misjudged your dose, there are no mulligans. Adding more complexity, there's also the tricky concept of "bioavailability." If you choose to inject THC intravenously as Lemberger did with his subjects back in the 1970s and Deepak Cyril D'Souza does with his at Yale, you can be sure that 100% of the dose gets into the person's bloodstream. That's much more efficient than smoking cannabis as we just discussed. With edibles, somewhere between 5% and 25% of the drug may make it into your bloodstream from your gut. But that amount varies significantly from person to person, depending on your individual metabolism, what else you have eaten recently, and other factors. If you really wanted to both increase bioavailability from the gut and reduce person-to-person variation, taking THC by suppository would be far more efficient. But it's not hard to predict that this is never going to be a popular trend and that the company that makes Preparation H is not destined to be a major player in the cannabis market anytime soon. Yankee ingenuity being what it is, weed entrepreneurs have harnessed the process of nano-emulsion to solve both the variable absorption problem and the frustratingly long wait time for edibles to do their thing. Thus, quick-acting edibles may be in our future. Next, let's move on from delirium to psychosis.

Short-lived, acute psychosis

What we saw happen to Arjun during Holi is a typical example of a very short-lived psychotic state. In simple terms, the word "psychosis" describes individuals who, while wide-awake (unlike delirium), have abnormal perceptions or beliefs. They may see or hear things that seem completely realistic to them but originate purely from inside their brain and not from any stimulus in the outside world (for example, they experience visual or auditory hallucinations). Other people, either in addition to hallucinations or occurring alone, have bizarre, irrational beliefs that

are both inconsistent with their own cultural group and impossible to argue the person out of because they are so utterly convincing. Such abnormal beliefs are termed “delusions.” In Arjun’s case, his brief psychosis was clearly precipitated by using a larger-than-usual dose of cannabis in the context of his personal worries and upsets (mental set). His symptoms disappeared within an hour or two with no treatment other than reassurance in the hospitality tent. In other instances, a different syndrome of more persistent psychotic symptoms following cannabis can last for days to weeks, as described next. These are the types of cases I mentioned earlier that are admitted to the psychiatric hospital at Ranchi in the month following Holi.

Persistent, acute psychosis

An example of persistent, acute psychosis is illustrated by a (composite) patient of mine. Twenty-year-old James smoked weed occasionally and generally liked the feeling it produced. It made him chatty and happy, somehow simultaneously relaxed and energized, and listening to music when stoned was always awesome. So when friends offered him a fatty of “really dank weed” before a concert, James didn’t think twice before indulging. And taking a couple of extra bong rips before the group hit the road. It was about a half hour into the performance when things began to feel a little off. The atmosphere felt charged with meaning, as if something superimportant were just about to happen. The feeling wasn’t exciting so much as menacing. The order of songs being played was definitely not random, and that, together with the way they were announced, made it clear to James that the band was referring specifically to him and the nasty breakup he’d had with Meaghan the month before—in a mean, snarky, mocking way. Not only was it obvious to him what was going on, but the entire crowd had clearly caught on to the message too. People around him were smirking, nudging each other, pointing at him, and signaling each other about him in a code of eye blinks and shoulder shrugs. The music from the stage was doing something very unpleasant to his brain, making it vibrate in a way that interfered with his thoughts. James had to get out of there in a hurry, and as he did so he experienced some kind of panic attack. His heart was racing, he felt shaky all over, his chest hurt, he was dizzy, and the whole concert hall felt unreal in a way that made him think he was going crazy. He made it back to his apartment and immediately took a few Xanax to help him relax and to sleep off whatever this was.

When he woke up at 3 a.m., things were worse. He now felt convinced that the neighbors were monitoring his every move and had somehow bugged his apartment. When he listened very carefully, he could hear some kind of subsonic whispering or chatter that he knew intuitively was coming from communication devices. James knew both that whatever was going on had to be illegal and that there was a police station two blocks south of where he was. So he snuck rapidly out of his apartment and made it safely to the precinct, despite the blue car that seemed to be following him. The police heard his story, recognized what was

likely happening, and persuaded James to accompany them to the local hospital's emergency department. He felt safe there. The psychiatrist on call interviewed him the next morning, when it was clear that the symptoms of paranoia from the night before seemed to have increased in intensity. James was alert—in fact hyperalert—visually checking out everything in the environment. He was absolutely clear that nothing like these experiences had ever happened to him previously. Although he spoke in a whisper to avoid being overheard, his speech was coherent, his memory unimpaired, and he was perfectly oriented in terms of knowing where he was, the day, and date, so this was clearly not a case of delirium. His neurological exam was squeaky clean. Blood and urine tests were positive for THC but no other drug. The psychiatrist acknowledged James's anxiety and distress; she offered him a low dose of an antipsychotic medication, which he accepted, but several hours later he seemed increasingly upset and agitated at the emergency-room staff "monitoring my thinking" and "messing with my mind." He now also refused to eat or drink because of suspicions that people wanted to "drug and poison me," and he refused further medication because "the problem is not with me, and I'm not the crazy one." It was now over 24 hours since he had smoked the cannabis. James continued to insist that the drug had nothing to do with his symptoms and that "all of this is really going on right now." The psychiatrist was able to persuade James to admit himself voluntarily to the psychiatry unit on the grounds that he would be safe there. His admission diagnosis was officially one of "substance-induced psychotic disorder (cannabis) with delusions, with onset during intoxication."

After several days of treatment with antipsychotic medications on the unit, all his symptoms began gradually to fade away, and James was able to accept that the cannabis had likely precipitated his symptoms. At times thereafter, he seemed a little unsure whether the experiences at the concert and subsequently had really occurred. But he was clear they had now ceased; and a few weeks later, he was back to baseline. Several months later, follow-up showed no return of any psychiatric symptoms. James was clear that what he'd undergone was extremely frightening, and he was equally insistent that he did not want to take the risk of using cannabis in the future.

Our fourth and last category of cannabis-associated psychiatric illness is the most serious, and it's the entity that most concerns legislators and public-health officials. Let's begin with a case vignette.

Chronic psychosis resembling schizophrenia

Janet (again a composite patient) was brought for psychiatric consultation and diagnosis by her parents, who'd been alerted by her roommates. Concerned about what they'd heard, Mom and Dad had flown in from California. Janet's friends had been troubled by several weeks of her increasingly withdrawn behavior, suspiciousness, failure to show up for weekly meetings in her graduate program, and a worrisome neglect of her personal hygiene, grooming, and eating.

Recounting their reunion with her in the apartment two days before, Mom wept in describing how Janet, who had always been rather prim and fastidious, had squatted down in front of her parents and nonchalantly changed her tampon. It was this startling and deeply upsetting change in her customary behavior more than her odd statements and preoccupations that pushed them to seek help for her.

What emerged from Janet's evaluation was that she had no family history of psychiatric illness and no known risk factors for psychosis. Her birth and development were unremarkable except for walking and speaking earlier than either of her sisters. She'd always been above average in IQ and mathematically talented. Janet skipped grades in school, took advanced placement classes in high school, and gained easy admission first to an undergraduate STEM program and most recently to a university graduate program in condensed matter physics in the Midwest. Placed with older kids in high school, Janet had begun smoking cannabis, most likely based on a number of factors. These included seeking peer acceptance, feeling relaxed and less socially anxious when using, helping her "get in the groove" and focus on programming, and experiencing music as more meaningful. In addition, her first serious high-school boyfriend had been a regular user. Janet's subsequent cannabis use had been steady over several years and heavy on weekends, but she was insistent that it had never adversely affected her energy or motivation or provoked any concerning symptoms. In the last few years, she had begun vaping cannabis concentrates but had tapered off and then discontinued use several months previously for financial and other reasons.

Careful questioning elicited the fact that her psychotic symptoms had probably started about a year previously. On her morning jogs, she had the strong sense there were coded messages somehow embedded in the refreshing breeze that blew from the lake. As she ran and the air currents swirled around her face and in her hair, there was an inescapable feeling that somebody somewhere was trying to convey important information to her. Initially she had no idea either what was attempting to be transmitted or its origin. From these relatively mild initial beginnings, the urgency, detail, and context of beliefs had multiplied to the extent that they preoccupied her almost entirely. Janet's delusions had now evolved to a state of extreme complexity, with bizarre ideas and beliefs nested systematically inside yet other delusions in a convoluted labyrinth of madness. She'd been savvy enough not to betray any of these frankly odd ideas to anybody else, even to close friends, but was surprisingly willing to talk about them when asked directly.

The basic story was this. When Janet was 7, an alien spacecraft had landed in a field near her parents' house. She had communicated with these beings, who had selected her from all earthlings based on her "talents and intuition" but had then "gone silent" until the last few months. At that time, they had recontacted her both telepathically and through coded messages in songs on the radio and TV advertisements. They could beam messages directly into her head and make their thoughts manifest, to the extent of making her think and do what they willed. (She had never mentioned the belief about the events at age 7 to anybody then or later, so this was likely a false memory or backdated delusional belief rather than

anything that had occurred to her at that time.) Janet had invested slowly increasing amounts of time and energy over many months in a quest to interconnect these alien messages, a series of meaningful coincidences in her life, and equipment data that she was analyzing as part of her graduate thesis on superconducting materials. She had concluded that as a test of her abilities and perseverance, she'd been placed in a form of programmed, simulated reality, where it was her task to puzzle her way out, make key logical connections, and solve an "extraplanetary algorithm." Ultimately her success would save humanity from a competing race of malign aliens. As part of this process, everyone around her including her roommates and parents had been replaced by extremely realistic-appearing fake doubles. What had begun as what seemed to her at the time a challenging and perhaps even exciting mission, however, had now devolved into a terrifying insoluble and inescapable web. Every car that passed by, every Facebook post, every plane that flew overhead only supplied additional confirmation that she was trapped. Because of her intelligence, Janet had managed to conceal her illness from her friends and parents for many months.

Once she was referred for psychiatric help, any logical attempt by the psychiatrist to question her delusional system was met with a seemingly logical counterargument. The truth of the old saw became apparent—it's impossible to argue someone logically out of a belief they were never argued into rationally to begin with. The alien-algorithm delusions were one major part of Janet's disorder. But alongside their development had been a gradual erosion of her sly sense of humor, vitality, get-up-and-go, enthusiasm for classical music, passion for sci-fi, interest in social relationships, appreciation of nature, and ultimately her daily self-care. Her parents said that she had lost her essential "Janet-ness" and that she seemed emotionally flat and somehow deadened. To them this erosion of her joie de vivre was far more distressing than any ideas about beings on other planets.

A thorough workup revealed that Janet didn't have a brain tumor or any obvious physical explanation for her psychiatric symptoms. There were no longer traces of THC or any other drug in her body. She was not delirious and had no mood disturbance to suggest severe depression or bipolar disorder. Janet met criteria for schizophrenia as a diagnosis of exclusion, since there was nothing else to explain her symptoms, and they had existed for a significant amount of time. Given her lack of a family history of psychosis or any other known risk factor for her disorder, the clinicians caring for her concluded that her significant use of cannabis since her midteens likely played a role in raising the odds that she would develop the disorder.

Janet responded reasonably well to several months of treatment with antipsychotic medications. Her web of delusions gradually dissolved, and she was able to return to her graduate program with a somewhat reduced work burden. But the medications failed to offer significant help for her shrunken liveliness and animation, diminished spontaneity, and blunted emotions. A peer support group, exercise program, and therapy with a trusted counselor helped manage them to some extent, however. She has not resumed cannabis use. Two years later, she has

not returned to baseline.

Acute human laboratory challenge studies

One obvious question is whether it is possible to reproduce psychosis symptoms in the laboratory by giving volunteers sufficient doses of cannabis or cannabinoids. The answer to this is a clear yes. A recent review [25] emphasizes the advantages of well-controlled laboratory research studies in allowing fine-tuning and oversight of dose, delivery, and proper characterization of administered pharmaceuticals compared to a placebo. This information should not be too unexpected, given the uncertainties and inaccuracies associated with tallying contents of marijuana purchased at dispensaries (and certainly on the illicit market), users' imprecise and subjective estimates of how much cannabis they consumed in a session, and distortions of memory related to recalling retrospectively how a particular dose of drug made them feel. Laboratory administration is also safer in that subjects can be observed and reassured when necessary by trained professionals. What happens to volunteers when we give them large doses of THC or other CB_1 receptor agonists under controlled laboratory conditions? It is clear that CB_1 agonists can mimic symptoms of psychosis. Randomized, double-blind, placebo-controlled crossover laboratory studies show that cannabinoid agonists, including plant-derived and synthetics, when administered acutely can mimic the subjective experience of psychosis in a dose-related manner. These psychotic manifestations can be evoked in otherwise healthy individuals. Such transiently produced symptoms include numerous negative, positive, and cognitive phenomena, including hallucinations, conceptual disorganization (confused thinking), perceptual distortions, delusions, emotional blunting and withdrawal, and slowed thinking and movement. These symptoms have a distinct time course, are related to dose, and are not explained merely by how sedated the subjects are. Deepak Cyril D'Souza vividly describes experiences of healthy individuals who were administered intravenous THC in his laboratory at Yale. One of his experimental subjects believed the laboratory clocks were being deliberately slowed down to confuse him, as part of the experiment. This seemed to be a delusional misinterpretation of subjective time slowing induced by the drug. Another subject believed, even after the drug infusion was long over, that THC was still being administered surreptitiously through the blood-pressure monitor. When it was taken away to allay his worry, he insisted the drug was being given to him through the bedsheets.[26]

A similar study was carried out by Marco Colizzi and his colleagues at the Institute of Psychiatry in London.[27] Sixteen healthy participants were given acute intravenous injections of just over 1 mg of THC and placebo on separate, randomized, placebo-controlled dose days. Twenty minutes following the THC injections, virtually every one of the participants had at least mild symptoms of psychosis, but fewer than one in five had moderate-to-severe changes. Similar to volunteers in the Yale studies, typical drug-induced symptoms included

conceptual disorganization, which affected almost everybody. For example, asked what an apple and a ball have in common, subjects gave illogical responses such as “You can eat the apple, but not the ball,” or “You can put the apple in the ball.” Other frequent symptoms that occurred in roughly half to two-thirds of subjects were hallucinations, suspiciousness, and paranoia. For example, one subject said, “The ventilator’s noise is louder . . . the noise is actually rain, it’s raining inside the room, I can see it and feel it, there is a black sky with seven blue drops.” Another volunteer stated, “What have you done to me? I understand, you want to make me paranoid with brainwashing questions.” Another said, “I feel I am all over the place and can’t stop laughing, thinking you will expose me, I will say something stupid or strange.” A lower percentage of Colizzi’s volunteers, roughly 20%–25%, also reported symptoms of grandiosity, hostility, and delusions. Quoted examples include “Is this real? Is this a fake interview made by a fake doctor, like a *Truman Show*?” and “I can understand things better and look for details, I am superior to others,” as well as “The injection changed me into someone with increased abilities,” and “I thought you were going to attack me, people are entering the room to check on me.” Compared to the placebo injections, these volunteers significantly increased their scores on standard symptom checklists used to gauge illness severity in patients with psychotic disorders. They also both reported and were rated by the researchers as having significant increases in negative symptoms of psychosis, including reduced rapport, lack of spontaneity, emotional withdrawal, and both concrete and stereotyped thinking. Here, subjects made statements such as “I can’t follow my thoughts, I’m not able to think,” or “I’m not interested, and I am not willing to talk, I don’t care,” and “My mind went blank, empty, with no thoughts.”

Dosing individuals with cannabis in a research laboratory does not mimic the usual social setting in which individuals self-administer the drug. There are strategies to address this problem. The University of Colorado Boulder (slogan: Be Boulder) will not allow cannabis to be consumed on its premises for research purposes, despite the drug being legal within the state for recreational and medicinal use. UC Boulder marijuana researchers therefore designed an ingenious work-around. Dr. Kent Hutchison and colleagues in the UCB psychology department use a research vehicle known as the CannaVan. This fully equipped motor vehicle, which is essentially a behavioral pharmacology laboratory on wheels, can be parked outside the research subject’s dwelling. A participant can then smoke their own supply of cannabis in their home and immediately walk outside to the van, where their blood levels of THC and CBD can be assessed, and they can take part in behavioral tests.[28]

THC certainly has psychoactive properties and can mimic both positive and negative symptoms of schizophrenia and psychosis. It’s worth emphasizing that nobody outside research laboratories chooses to take THC intravenously, but it would be instructive to look at blood levels of THC and its major metabolites compared to individuals who inhale concentrates through dabbing, as these conceivably could be similar. Similar experiments show transient symptom

worsening in individuals with schizophrenia, even in those taking antipsychotic medications.[29] So, what are the underlying biological mechanisms by which the drug is producing these effects?

How might THC cause psychosis?

Researchers are beginning to document how cannabis use impacts the endocannabinoid system, but how cannabis increases risk of psychosis is not yet well understood. One obvious hypothesis is that acute THC challenge results in dopamine (DA) release, and the DA hypothesis of schizophrenia argues that so-called positive symptoms of psychosis such as hallucinations and delusions are due to excessive brain dopamine in particular neural circuits. The dopamine hypothesis is based on several observations. Drugs that cause dopamine to be released from neurons in large quantities or to build up inside neural synapses, such as amphetamines and cocaine, can precipitate psychosis if taken in sufficiently large quantities. Second, all known antipsychotic medications block DA receptors. Third, most never-medicated schizophrenia patients, when given intravenous amphetamine, release excessive amounts of pre-synaptic DA, as evidenced on PET scans. Last, at least for first-generation antipsychotic drugs, the more powerful the medication at blocking DA D_2 receptors, the lower the average dose of the drug needed to be effective in ameliorating positive psychotic symptoms. Or in simple terms, the more powerful the drug is in blocking DA, the less of it is needed for an effective dose. It's important to understand that use of the word "positive" in this context implies not good and desirable but the addition of some phenomenon not normally occurring to one's mental life. In other words, "positive" is shorthand for "extra, unusual mental events." In the same way, "negative" psychosis symptoms refer to the subtraction of something normal from mental life, typically emotional range, enthusiasm, or whatever it is that helps us get out of bed in the morning. The presence of these negative symptoms of schizophrenia is what was so upsetting to Janet's parents.

DA-containing neurons are located in different parts of the brain. We encountered them previously in reward circuits in Chapter 4 and in midbrain movement and sleep centers in the psychology section. We saw there that these DA neurons interact with the ECS in multiple ways. Many DA cells communicate with (or, in the case of some reward regions, are members of) the striatum, so named because parts of it are striped. The striatum consists of a number of deep brain nuclei that are the input to the remainder of the basal ganglia, many of whose cells are modulated by DA. If the DA hypothesis of cannabis psychosis is correct, then we would expect THC to release measurable amounts of DA in this region. In other words, the hypothesis would be that cannabis or constituent chemicals such as THC would act analogously to amphetamine, as mentioned earlier. That simple, straightforward conjecture turns out not to be the case. Human PET studies from Sagnik Bhattacharyya and Robin Murray at the Institute of Psychiatry in London, UK, show that acute administration of THC releases only unimpressive amounts

of striatal DA and also that striatal DA is low in chronic cannabis users.[30] Similarly, studies disagree as to whether drugs that block DA receptors (such as DA D_2 receptor antagonists like commonly prescribed antipsychotic medications) reverse acute psychosis-provoking effects of THC in healthy subjects. Certainly, effective long-term treatment with antipsychotic drugs does not prevent an acute THC challenge from causing a flare-up of positive symptoms in patients with chronic schizophrenia.[29] Interactions between the cannabinoid and glutamate neurotransmitter systems have also been proposed as a mechanism whereby cannabis triggers psychosis.[25] Evidence for this conjecture is mainly from animal experiments, but also supporting the idea are some human spectroscopic data, where accurate chemical measurements have been made using an adaptation of MRI scanners that can tune into and measure amounts of brain molecules.[31] But there were no clear answers until recently. As we reviewed earlier, Ansel Hillmer at Yale had volunteers smoke a joint while in a PET scanner. Using a rather creative research kinetic modeling design, and focusing on the striatum, he was able to show convincingly that the cannabis caused significant dopamine release.[32]

Amotivation: As the old joke states, "People say nothing is impossible, but I do nothing every day." Separate from the issue of chronic psychosis, some studies suggest that chronic cannabis use is associated with persistent psychosocial problems such as impaired school and occupational performance that overlap with negative symptoms. It's often suggested that these difficulties may be due to chronic drug-related effects on either thinking or motivation. The stereotype of a 1960s hippie reclining on an eastern-themed cushion listening to acid rock or of a contemporary stoner with terminal couch lock living in his parent's basement and driven to do little more than play video games and eat junk food is a trope familiar to all of us. In fact some precursor of this cliché dates back at least to the 18th century, when tales of torpid, impoverished, unemployed Egyptians poleaxed by hashish entered the popular imagination. The 19th century Indian Hemp Drugs Commission also reported that heavy cannabis use was associated with reduced motivation. The term "amotivational syndrome" is frequently applied to this state. It is supposedly characterized by detachment, loss of drives and ambition, lethargy, flat emotions ("like, whatever man"), and impaired working memory, attention, and judgment. Is there any truth behind this stereotype? And if people with the supposed syndrome quit cannabis use, does the presumed amotivation disappear, or does it persist?

We immediately run into another chicken-and-egg problem. For example, if you start off life with low socioeconomic status or chronic poverty and find it a struggle to get even a low-paying job, then chronic intoxication may appear to be a reasonable life choice. One way to try and dissect this conundrum is to bring volunteers into the laboratory and to dose them for prolonged periods of time with cannabis and see what happens. Setting aside the legal, ethical, and logistical problems involved with this, we could conduct such a hypothetical experiment and try to assess whether the overall motivation of our subjects begins to dwindle. If it does, then is it dose-related? A more feasible approach might be to find a

population of chronic cannabis users and to withdraw them from the drug under controlled circumstances. Do they gradually morph into Energizer bunnies? And if not, does that reflect their baseline pre-drug state or presumed irreversible brain damage due to chronic cannabis toxicity? Animal studies shed some light on these questions, as they provide a situation where previously drug-free subjects can be dosed chronically over a long period of time compared to placebo. Such investigations also help dissect motivation from cognitive issues. In other words, does an animal chronically given cannabis not perform well on a task because of impaired learning or because it just can't be bothered to engage? Mason Silviera and his colleagues at the University of British Columbia in Vancouver investigated this phenomenon of cognitive effort by treating male rats with acute doses of THC, CBD, and both drugs together. The rats had been trained to perform both a more difficult, challenging task to earn a large sugary reward and an easy low-payoff task. THC administration resulted in the rats becoming what the investigators described as "cognitively lazy." They were still perfectly able to complete the cognitively demanding task (their accuracy, attention, and decision-making were fully intact), but essentially they couldn't be bothered to try. In other words, on THC they didn't give a rat's ass. Interestingly, their altered performance correlated with CB_1 receptor density in their little ratty prefrontal cortexes. Since these drug exposures were acute, they are not particularly informative about chronic effects. Experiments from the early 1990s involving chronic exposure of rhesus monkeys to marijuana smoke showed some modest effects on reducing motivation, but these were not definitive. Overall, the evidence for an enduring human cannabis-related amotivational syndrome seems to be equivocal or not very strong.[33–36]

Let's return to cannabis psychosis and its underlying biology. Another route to understanding how cannabis might be related to psychosis comes through an examination of the brain's electrical activity. Whenever any of us encounters something in the environment that's either different or seems significant, our brain fires off a characteristic signal one-third of a second later. This brain wave, known as the P 300, occurs in all mammals and is basically a "surprise" or salience message saying, "Hey there—pay attention! Something important may be going on here." If you are connected to an EEG machine, an experiment as simple as listening to a series of regularly spaced beeps through headphones can elicit a P 300 wave for each occasional beep that's a little different from the rest. To test the hypothesis that the P 300 is found universally across the mammalian kingdom, one of our former junior faculty went to the local aquarium and gently attached an EEG electrode the size of a toilet plunger to the head of a cooperative killer whale. The whale was provided with a series of identical underwater click sounds with occasional slightly different-toned "oddball" clicks. The whale responded to the latter by generating a classic P 300 response.[37] Reductions in the size of the P 300 peak are often seen in people with psychotic illnesses, although this finding is rather nonspecific and also associated with several other disorders. Drops in P 300 magnitude are provoked by cannabinoid agonists such as THC. Interestingly, the

size of those falls for different cannabinoid compounds correlates closely with their psychosis-mimicking effects. Some researchers have theorized that particular cannabis-mediated disruptions in EEG frequency synchronization patterns between distant brain areas might also be related to positive psychotic symptoms.[38] At Yale, Jose Cortes-Briones[39] hypothesized that positive psychosis-symptom-like effects of acute THC doses are associated with increased cortical "noise" (defined as EEG randomness levels) in healthy human volunteers. Because EEG data are much cheaper and more straightforward to collect than approaches using MRI or PET scanners, using them probes an area of cannabinoid research that we will likely see more of in the future.

Dual diagnosis patients

For reasons that are not well understood, people who already have schizophrenia are at increased risk of subsequently developing substance abuse disorders of all sorts (at a rate almost five times that of the general population). This includes cigarette smoking and cannabis use. Part of what accounts for these increases is that people with schizophrenia have a tendency in general to make disadvantageously risky decisions and an unfavorably altered balance in their ability to process delayed rewards and punishments. These factors tend to push them in the direction of substance use more generally. But let's focus just on cannabis. One simple hypothesis for increased cannabis use in schizophrenia seems to be that such patients are seeking short-term relief from symptoms and a boost in mood. They don't think too much about the later consequences of an increased likelihood of a relapse, worsening of their hallucinations and delusions, and more frequent illness recurrences that also accompany their cannabis use.[40,41]

Schizophrenia treatment trials with cannabidiol (CBD)

So, what are we to make of the observations on THC and psychosis that we have just reviewed? Let's integrate them with some additional important information. First, the DA hypothesis of schizophrenia fails to explain some significant features of the illness. About one in three patients diagnosed with schizophrenia does not produce excess amounts of pre-synaptic DA when challenged with amphetamines prior to any physician-ordered treatment. Antipsychotic drugs that block DA receptors can interfere with these measurements, so it's important to conduct such DA studies on never-medicated patients. Consistent with those data, one in three patients with schizophrenia pretty much fails to respond to DA-receptor blocking antipsychotic medications. The obvious implication is that nothing is wrong with the DA system in these individuals. Thus, something else is likely causing their illness. Second, there may be something awry in the ECS of people with psychosis, whether or not they have ever used cannabis.[42,43] There actually is evidence for that hypothesis. Such changes detected to date in patients with schizophrenia include altered levels of the endocannabinoid ligand anandamide in their cerebrospinal fluid.[44] The status of such ECS abnormalities is currently

unknown. Are they an integral part of the illness or some secondary phenomenon? Do they affect some patients with schizophrenia or all of them? An obvious question is whether somehow intervening to redress such a brain endocannabinoid imbalance might help treat schizophrenia symptoms. This idea occurred to several schizophrenia clinicians and researchers pretty much simultaneously. Since THC and other CB_1 partial agonists can provoke psychosis, and CBD has opposite effects in the human brain to THC under a number of circumstances,[45] then CBD suggests itself as an obvious strategy for treating patients with psychotic illnesses, including schizophrenia.

Furthermore, the argument is often made that 1960s-style cannabis was "safer" from the point of view of psychosis risk because it had a significantly lower percentage of THC and correspondingly higher percentage of CBD. Because CBD is a relatively safe compound with almost no side effects, treatment trials in patients with schizophrenia seem appealing and low risk. Early results in small preliminary pilot studies seemed to augur well. Encouraged by these reports suggesting that CBD had antipsychotic effects,[46] a recent study from the UK by Philip McGuire[47] conducted a clinical trial where a random 50% of 88 individuals with schizophrenia were maintained on their baseline antipsychotic medication while adding 1,000 mg of oral CBD capsules daily for six weeks. The other 50% of his patients received placebo capsules. Those given the active drug experienced significant improvements on measures of positive psychotic symptoms (such as hallucinations and delusions) and on their clinicians' impressions of the patients' improvement and illness severity, compared to those who got placebo. The patients who received CBD also had a tendency toward improvement in cognitive tests and in their overall functioning. A carefully executed attempted replication by Douglas Boggs[48] at a somewhat lower CBD daily dose (600 mg/day), however, failed to demonstrate any therapeutic effect at all in 36 schizophrenia patients compared to placebo.

Recently, the Maudsley group, including Robin Murray, Sagnik Bhattacharyya, and Philip McGuire, looked at the effect of CBD administration in 33 individuals who were starting to show symptoms of psychosis but not yet enough of them to qualify for a diagnosis of schizophrenia.[49] Nineteen healthy control subjects also participated. All participants received a one-time single oral dose of either CBD or placebo. People in the early psychosis group were felt to be too sick or too paranoid to go into the MRI scanner on two different occasions. Thus the study design entailed subjects not being their own controls. In other words, each subject, whatever their diagnosis, received only one pill (either CBD or placebo) once. After receiving the medicine (or placebo), subjects went into the scanner and engaged in a gamelike task for which they received a reward of money if they could respond to stimuli fast enough. The main finding of the study was that a single dose of CBD in the high-risk psychosis patients changed brain activity in several regions that included the striatum and other areas. In each of these regions, the brain activation levels for the psychosis risk group on CBD was somewhere in between the response of the healthy control individuals who received no drug and

the remaining psychosis-risk patients who received placebo. Although less than ideal in design, this experiment implies that CBD may be tending to normalize dysfunction in selected brain regions, all of which we have noted are implicated in psychosis. This in turn may suggest at a brain level how CBD is exerting its therapeutic effects.

Currently a giant question mark hangs over this whole area of potential treatment. Since CBD is relatively inexpensive and has few side effects, it could potentially benefit thousands of patients with psychotic illnesses. Until there is convincing evidence that it actually works as hoped, however, this remains a theoretical possibility.

Are there biological differences in individuals with psychosis who have histories of significant adolescent cannabis use?

Some related questions, such as how many individuals would we have to keep away from cannabis to prevent one case of schizophrenia, and what population risk assessments tell us about the major cannabis-related risks for psychosis, were discussed in Chapter 6. As a follow-up to those issues though, let's look at some studies that address the underlying biological differences between individuals with psychotic illnesses with and without prior heavy cannabis abuse histories. One research strategy has been to examine the "fifty shades of gray matter" question. For example, one study investigated over one hundred individuals with various psychotic disorders and looked at their histories of cannabis use.[50] Using structural MRIs, scientists contrasted the density of gray matter in the brains of people with schizophrenia and psychotic bipolar disorder with and without a history of adolescent cannabis use. As many previous MRI studies in psychotic individuals have shown, the patients as a whole had lower total brain and regional gray-matter density compared to healthy controls. Interestingly though, patients who had used cannabis in adolescence had significantly lesser gray-matter reductions, an effect that was particularly prominent in schizophrenia. Similarly, Hanna[51] compared scores of cognitive abilities in approximately one hundred psychotic individuals from the same psychosis study to healthy controls. Cognitive-test abilities were significantly higher in patients with histories of adolescent cannabis use compared to those without prior cannabis use. Again, this effect was significant only in schizophrenia. Together, these results are consistent with a hypothesis that early cannabis use may precipitate psychosis in those who had less prominent risk factors in the areas of compromised cognition and brain anatomy before they became sick. It is also possible that adolescent cannabis use could be illuminating a distinct psychosis subgroup who show typical psychosis symptoms but whose illness is associated with a lesser degree of cognitive and brain structural damage.

Let's move on from a consideration of psychosis into the territory of addiction.

How do we define "abuse," "dependence," and "substance use disorder"?

"Substance abuse" (as in the American Psychiatric Association's *Diagnostic and Statistical Manual* version IV-TR),[52] is generally defined as drug or alcohol use that is maladaptive, in the sense of leading to clinically significant impairment or distress as manifested by school problems, physical hazards (such as DWI), legal problems (for example, arrest for disorderly conduct), and continued use despite recurrent social problems (for example, physical fights). "Substance dependence" includes all of the above plus the development of tolerance (needing to use more and more of the substance to get the same effect), withdrawal effects when the substance is stopped (such as feeling significantly anxious or having sleep disturbances or the shakes), as well as possible compulsive use. In addition, dependence can include features such as using more of the substance than intended; trying to quit but failing to do so, especially in the face of knowing that the substance is causing problems (such as depression); and using the substance takes up more and more of the person's time and attention so that other activities, such as schoolwork and intimate relationships, suffer. "Binge drinking" is defined on one hand by intent—that is, using alcohol with the primary intention of getting drunk—and on the other hand by physical quantities—that is, ingesting (somewhat arbitrarily defined) large quantities of alcohol (five alcohol units for men or four for women) in a short period of time (three hours).

The broader term "substance use disorder" has multiple definitions, including abuse and dependence, but for alcohol this term sometimes also encompasses bingeing. More recent versions of the *Diagnostic and Statistical Manual*, such as the fifth edition (first issued in 2013), de-emphasize the separation of abuse and dependence. They opt instead to consider all the above symptoms and to then classify any substance use disorder across a broad range of seriousness ranging from mild to severe.

When do these issues first tend to manifest? Adolescence is a high-risk period for beginning alcohol and substance use and for substance-related problems. The biological mechanisms that might explain why some people can use substances in moderate amounts without apparent problems while others transition to problem use are only partly understood. Some of substance abuse is genetic (about 50% is the accepted figure), and the rest environmental. For example, if you live in a "dry" US state where alcohol is hard to obtain, that environmental factor has a profound effect on alcoholism rates. It's precisely this sort of statistic that worries opponents of recreational cannabis legalization. Their concern is that increased access leads directly to both greater use and subsequent diversion of the drug to vulnerable teenagers. Teenagers are felt to be particularly vulnerable as a class because their brains are still developing actively into their 20s. Brain connections are being sculpted in all sorts of ways in the service of greater neural efficiency. More "mature" future-directed frontal-lobe functions gradually predominate over more "immature" emotion-driven, impulsive limbic circuitry. Given the known role of the ECS in brain development, including neural pruning, which we reviewed in Chapter 4, the concern is that cannabis and synthetic cannabinoids will interfere with these adolescent developmental processes—to the long-term

detriment of brain development. The hypothesis is that younger brains are more vulnerable and that substance use actually alters their developmental trajectories. This is well established for cannabis in animal models,[53,54] but much less certain in humans. As we reviewed in the epidemiology section, there is uncertainty whether young people who begin cannabis use before they reach 18 suffer permanent cognitive decreases. But short-term deleterious effects of cannabis on cognition are better documented. Certainly, students who smoke cannabis during college end up with lower GPAs.[55–59]

The genetic half of substance-abuse risk may be mediated through different kinds of inherited physiological response to the drug. These could include variation in the enzymes that metabolize a substance or the brain receptors that it binds to. In addition, the complex of genes that conveys the personality type of being impulsive, disinhibited, sensation seeking, and reward driven seems relevant. Possessing this variant of impulsivity is associated with more frequent substance use, in greater quantities, and with more negative consequences.

Substance-use patterns, particularly for alcohol, peak during the late teens and early 20s when individuals are more open to exploring new activities and less worried by long-term consequences. Using substances for the first time peaks at age 18 and is mostly over by age 20. Freshman year is a time of exploration, and significant substance use is a part of this process for many college students. At least for alcohol, the highest prevalence of dependency is seen in 18- to 24-year-olds, after which young adults seem to "mature out," and many stop using entirely or severely moderate their substance use. College is an interesting environment for substance use, in part because it's a safe ecosystem that can reduce the consequences of binge drinking or weed smoking. Certainly while there, students experience rapid increases in substance use. Since two-thirds of college students report consuming alcohol in the past 30 days, heavy alcohol use could be considered normative (although illegal). After alcohol, marijuana is by far the most frequent substance of choice among college students. National surveys of 18- to 25-year-olds report over 50% lifetime cannabis use, with one-third of individuals in this group using in the last year and one in five in the last month. Furthermore, 60% of alcohol-drinking adolescents report using alcohol and cannabis simultaneously. Heavy recreational substance use impacts college achievement and likely cognition. Students who are intoxicated or hung over are more likely to miss classes, fall behind in schoolwork, and get poorer grades. They may be less motivated to study, have fewer opportunities to study (because they are out carousing), or have more difficulties when they do attempt to study because they are hung over or perhaps exhibit longer-lasting cognitive impairment.[60] These relationship patterns are well established for alcohol use but more certain and decidedly less studied for cannabis. Hints about what might be going on come from a variety of sources, but college students are a natural place to go to seek this information. Let's look at some examples.

A Dutch team investigated how legal cannabis access affected student performance under a set of unique circumstances. The city of Maastricht in the

Netherlands declared a ban on allowing university students to purchase cannabis at its licensed marijuana shops. This prohibition started on a known date, so it was straightforward for the researchers to explore academic grades of local students before and during its implementation. Interestingly, and likely celebrated by Dutch parents, the academic grades of students who could no longer legally purchase cannabis increased significantly. Given what we know regarding freshman substance use, it's unsurprising that these academic improvements were driven by younger students. Perhaps less intuitive is that the effects were more marked for women and individuals with lower grades. The newly abstinent student body showed the biggest grade boosts in courses that demanded more numerical and mathematical abilities. The research team dissected the students' course evaluations and concluded that their improved performance was due to understanding the course material better as opposed to bucking up their study habits.[61]

A dozen years ago, funded by the National Institute on Alcohol Abuse and Alcoholism (NIAAA), I organized the Brain and Alcohol Research in College Students (BARCS) study. We examined over 2,000 freshmen students admitted to Trinity College and Central Connecticut State University over several successive years. Such a sample size is decently powered to answer some major research questions. Including students from two demographically different colleges with varied populations made the results more generalizable. The study was designed with two goals in mind. The first was to search for predictors—to identify which of these 18-year-olds was at increased risk for substance abuse and dependence before this occurred. The second was to examine consequences of substance use once it did occur. For example, what effects (if any) did two years of binge drinking or heavy cannabis use have on mood, college grades, IQ tests, brain structure and function, and EEG patterns? Because alcohol and marijuana are the two most abused substances in US colleges, we were interested in capturing not only their individual effects but also their combined influences, and not only at one moment in time but also over the span of two years. We managed to recruit 99% of each incoming class as study participants. At the first study visit, the students had cognitive testing (on 16 different tasks) and assessments of 10 measures of impulsivity, and they told us about their current alcohol and substance use. The study subjects underwent psychiatric diagnostic interviews, gave us information about their family histories of alcohol and drug use, provided their own prior academic and substance use histories, and donated a DNA sample. They also told us unique facts about themselves that we used subsequently to confirm their identity in later online questionnaire sessions. What was the name of your favorite pet when you were aged 5? How many brothers and sisters do you have? And so on. Soon thereafter at their second study visit, 450 randomly chosen students underwent structural and functional MRI scans, computerized impulsivity testing, an EEG, and an even more detailed structured substance-abuse interview. Each month thereafter for two years, all 2,000 research volunteers went online to a highly secure study website, using individualized passwords, to fill out detailed

information about their drinking and drug use. We explored the quantity and frequency of use. For example, a student might endorse the statement “In the last month I got high twice a week, used a gram of cannabis flower each time.” We also tallied consequences of intoxication, such as “I binge drank and got into a fight twice, was stoned and had unprotected sex once.” The students also told us about their mood and anxiety levels and sleep patterns. We confirmed that it was the subjects themselves, and not, for example, their roommates, who were completing each monthly survey through their correct answers to a few of the many personal-identifier questions that we had asked them at the first interview. If they provided a different name for their pet goldfish at age 10, we noted that. We carefully tracked these students’ college grades each semester. For those who had MRI scans, we first acquired a detailed structural MRI then measured their resting state fMRI. In addition, while in the scanner, they completed a virtual maze task that measured their spatial-location abilities; they completed a visuo-spatial measure by recalling abstract shapes; they performed a task to assess impulsivity; and they were shown alcohol and soft-drink cues while we looked at their brain’s response. Our interest in spatial and visuo-spatial measures was prompted by the fact that the hippocampus plays an important role in mediating these skills and that this brain region may be especially vulnerable in teenagers to the effects of both alcohol and cannabis.

At the end of two years, everything our subjects had completed at the study’s beginning (except for the DNA test) was repeated. For example, if he or she had had an MRI session at the start of the study, then that was repeated at 24 months. What did we discover? When we explored substance-use patterns, three clusters of students emerged. The first was a group of students who rarely drank and seldom if ever used marijuana. Let’s call them near-teetotalers or substance virgins. The second was a group of individuals who drank moderate to high amounts of alcohol but used little or no cannabis. Third was a cluster of students who used medium-to-high amounts of both substances. To my surprise, the expected group of pure stoners who got high on cannabis on a regular basis but disdained alcohol barely existed at these two colleges. While I knew many such people back in the ’60s, they were an endangered species in our college sample. The three substance-use groups started off with highly comparable precollege standardized test scores (SATs, etc.). In the first semester, the second group of freshmen (moderate/high alcohol, no/low cannabis) had lower academic grades than the first group (near-teetotalers). The differences between these two groups dwindled away over time so that their grades became comparable. In contrast, the third student group (those who used medium/high amounts of both alcohol and cannabis) not only scored lower in the first semester but also had consistently lower grades across the entire two years we followed them. As our Dutch colleagues in Maastricht had found for cannabis, our students who curtailed their substance use over time had significantly higher academic GPAs than their colleagues who maintained their high levels of alcohol and cannabis use.

What could we say about the effects of heavy cannabis use alone on academic

grades? In this case, absolutely nothing. That was because the ’60s stereotype I had conjured up—a group of red-eyed students clustered around a bong saying things such as “I never drink booze, alcohol tastes bad, it makes people aggressive, it’s an addictive poison, it killed my granddad,” and so on—was as rare as hen’s teeth. And therefore the study couldn’t yield meaningful data on this question.[62] But, that’s science for you. You go out and carefully recruit a large diverse sample, study them in great detail, and find out that one of the more interesting questions you wanted to address is not answerable. This certainly doesn’t mean a study is fatally compromised—just that most data sources, including this one, are necessarily incomplete in some respect and that alas no research is perfect. We accepted that our sample was the best data source we had for now and strategized how to improve our design the next time around. Incidentally, our missing cannabis-purist/alcohol-disdaining college students certainly exist currently in other contexts. I have met them in Colorado and in California. For whatever reason, such individuals didn’t make it into the freshman classes we studied in Connecticut.

In general, exactly as in our study, teens and young adults who use both alcohol and cannabis have worse performance than near-abstainers on tests of complex attention, memory, processing speed, and visuo-spatial functioning.[63] Groups don’t tell the whole story, however. Many of us have come across individual heavy substance users who are seemingly immune to the expected deleterious effects, perhaps due to genetic luck that has equipped them with resilient constitutions and healthy adaptive physiologies. People like our case example Janet, who can consume large amounts of cannabis and maintain respectable GPAs, certainly exist, because heavy cannabis use is a population or group risk for college grade decline, not an absolute determinant for an individual. Cannabis smokers won’t like the analogy, but significant numbers of people smoke a couple of packs of cigarettes a day for years until late life and never develop lung cancer. Certainly, rats can develop behavioral and brain tolerance for heavy marijuana use so that its cognitive and other effects diminish over time.[64] All these observations undermine a simplistic “cannabis rots your brain” message, but they do not entirely negate it.

Disordered use, dependence, and addiction

A subpopulation of mainly young individuals misuses cannabis, finds it hard to quit, and develops addiction or dependence. As with all substances for which there is problematic use, it is not only the THC that constitutes the problem but both the relationship the individual has with the substance as well as idiosyncratic reactions some individual users experience as a result of using the substance. Let’s look at another case to understand what goes into the mix here.

John is a 22-year-old man employed in the “gig” economy in car repair. He works for a local garage and for friends on a cash-only basis. John is brighter than average, and as a young teen he wanted to become an engineer and work at the

local aircraft plant, but he dropped out of school in the 10th grade due to a combination of factors. He began using cannabis at age 14 with his school friends; as a result of which, he found he was less inclined to study for school and less able to absorb lessons, and he attended school less often. He also noticed that over time he needed to use more cannabis to reach the same level of "high." His grades slipped, and he received several academic warnings but managed to hang on. Things were tough at home. His mom drank. His dad worked hard, hung out with his buddies a lot, and was emotionally unavailable. When his parents were together at home, they often fought, and smoking weed made him comfortably numb when they'd scream at each other. Nobody noticed things were going worse for John in school, and nobody was concerned that he might have a substance use problem. John was arrested a few times for possession of small amounts of cannabis, occurrences made several times more likely by his ethnic-minority status. Chat with him, and he will tell you readily that his current favorite leisure-time activity is smoking weed, using the "ODB" (old dirty bong) in his living room. John's definition of "leisure time" is pretty elastic and includes bong hits first thing in the morning after getting out of bed, multiple times during the day, and before going to sleep at night. Getting high might not be at the exact center of his life, but it's pretty close and certainly up there on his priority hierarchy. A few months ago, he was really motivated to quit cannabis when his longtime girlfriend gave him an ultimatum: cut back on your use if you want to stay in a relationship with me. He tried several times, but on each occasion, events unfolded in pretty much the same way. He was fine for maybe a day or two, then he would find himself getting angry and irritable, lose his appetite, and develop a throbbing headache. Getting to sleep at night was a huge struggle, and once he could sleep, he'd experience odd and disturbing dreams. His mood would go down a couple of notches, and his mind would feel anxious and restless. He described the state as "sort of being like caffeine withdrawal but scaled up a whole lot" and "not quite as bad as trying to quit cigarette smoking." Nevertheless, each of the times he tried to quit cannabis, after a few days of discomfort and sleep deprivation, it just felt a whole lot easier to go back to smoking the ODB. Once you gravitate to old habits you tend to stay there. John's relationship with his girlfriend did fall apart, and he doesn't like to dwell on where his life actually is compared to the engineering job he once wanted. Still, stopping cannabis use just seems out of reach at this point. He's also concerned, at least sometimes, that all those years of cannabis smoking may have impaired his memory and motivation so that engineering training may be out of the picture forever.

Several things about John's cannabis addiction are typical. He has a probable family history of alcohol abuse in his mother and several of her relatives, and many of the kids in his school and neighborhood were cannabis users, so both genetic and environmental factors may have pushed him in that direction. His arrests for marijuana possession might have reinforced a feeling of being victimized. Minority-group arrests for cannabis are significantly disproportionate despite similar cannabis use rates in Caucasian and non-Caucasian populations.

But John's brushes with the law occurred before the age of 18 years and were not accompanied by any referral to teen substance-abuse programs, and thus they in no way deterred his further cannabis use.[65] Multi-times per day use of cannabinoid agonists such as THC is believed to retrain brain areas related to habits (such as parts of the basal ganglia) and to down-regulate brain CB_1 receptors as measured by PET. It's thus unsurprising that quitting is hard when your brain is pulling you toward continued use. Stopping heavy cannabis use won't kill you, as can happen with alcohol (which can cause delirium tremens, or d.t.'s, and alcohol withdrawal seizures have significant mortality). Nor is it even nonlethal-but-massively-unpleasant, as going "cold turkey" from opioids can be. Nevertheless, cannabis withdrawal can be sufficiently dysphoric to deter quitting in a significant number of people who try.[66,67] Cannabis withdrawal is also clinically significant "because it is associated with functional impairment to normal daily activities, as well as relapse to cannabis use." [68] Interestingly, cannabis withdrawal was first taken seriously only when the CB_1 antagonist drug rimonabant was administered to regular cannabis users. It rapidly precipitated significant withdrawal symptoms in a number of them. A well-written first-person account of marijuana addiction is Neal Pollack's essay "I'm Just a Middle-Aged House Dad Addicted to Pot." [69]

How prevalent is cannabis dependence? According to the National Institute on Drug Abuse, somewhere around 9% of users become dependent, and that number doubles or perhaps even triples for those who start heavy use before the age of 18. To put that in perspective, these numbers are certainly lower than figures for alcohol addiction but still very concerning. Even if the majority of people who use marijuana don't go on to use other harder drugs like opioids or cocaine (and most don't), the worry is that if recreational cannabis is legalized nationally, then the drug will be diverted into the hands of teenagers, and that 18%–27% figure will apply to a much larger total number of adolescents. As we saw in Chapter 6, actual rates of adolescent cannabis use have stayed steady, even in states that have legalized medical and recreational cannabis. But the existing percentages are much larger than anyone would want, even though cannabis is much lower down on the list of harmful substances than alcohol, prescription opioids, and tobacco. An Australian study suggests that dependent cannabis users were more likely to be aged 18–24 years old, to be unemployed, and to have higher levels of depression than nondependent users.[70] Some pharmaceutical companies are trying to test drugs that alter cannabinoid-receptor and ECS-enzyme levels to ease the discomfort of cannabis withdrawal. It would be helpful if these efforts were successful, because currently no pharmaceutical or behavioral approach tends to be terribly effective for this purpose.[71] John's concerns regarding long-term effects of cannabis on his motivation and cognitive abilities are not without foundation. A study of US postal workers found lower level of attainment among people who tested positive for cannabis,[72] although again that begs the chicken-egg question. Outside of acute effects on cognition, long-term use may affect cognitive skills, making it harder to learn and retain information.

Individuals like John who consume cannabis multiple times throughout the day

are not rare. A proportion of them continue use into their 30s. John Hughes and his colleagues in Vermont[73] recruited 142 daily marijuana users through advertising and followed them daily for three months using an interactive voice-response phone system. Briefly, the mean age of the subjects was 33, just under half were employed, 60% were women, and one-third had less than a high-school education. The participants used marijuana just over three times daily on average. Almost 75% of them used tobacco, and almost all used some alcohol (four to five drinks a week, with about one-third binge drinking once a month, which was pretty similar to the national average for adults in the same age range). The take-home message of this study was that nearly all the participants were subjectively chronically intoxicated. They apparently had not developed substantial tolerance to being stoned and were affected by cannabis when awake pretty much whenever the researchers checked in on them.

An important question regarding cannabis abuse and dependence is what determines who is at risk and who is protected. Brain-related factors hypothesized to be crucial in underpinning abuse liability may include an imbalance between the neurotransmitters DA and glutamate in the brain's reward system. The two being out of whack may lead to a "reward deficit syndrome" (RDS). Having a positive family history of any type of substance abuse may be a nonspecific bias toward increased likelihood for marijuana (and other substance) use disorder via this biochemical vulnerability. The conjecture posits that for people with RDS, it takes more reward input to float the affected person's boat because their reward signals are blunted. Therefore, so the hypothesis goes, such individuals seek extreme stimulation just to reach the satisfaction level that most of us feel at baseline. Thus, reward deficiency syndrome may be expressed as amped-up thrill seeking or sensation seeking. Substance use may be one form of behavior through which this tendency manifests, but high-stakes gambling, hang gliding, or extreme rock climbing may be behavioral equivalents. My research group has looked carefully at impulsivity as a risk factor for alcoholism, including in our BARCS freshman-student sample. One of the tasks we administered to subjects in the MRI scanner tapped into this propensity. We determined that a combination of impulsivity plus compulsivity traits seems to be such a risk factor. We hypothesized that the first tendency (impulsivity) gets a person started with substance use and the second (compulsivity) keeps them coming back for more. This raises the general issue that whatever constitutional, personality, or environmental factors first encourage an individual to try a drug may be very different from those that maintain use. Some of the latter determinants include exposure to childhood trauma and abuse, and availability of the drug in one's environment. If you are an astronaut on Mars and there is no weed available, then obviously you're not going to be able to use any. Unless of course an enterprising interplanetary dispensary gets there ahead of you. Additional factors pushing a person toward substance use include being anxious or depressed, beginning use early in life (early habits tend to persist), and biological sex. In general, men tend to score higher on sensation-seeking scales and seem overall more vulnerable to substance abuse of all types. On the other

hand, women, once they begin abusing marijuana and other substances, tend to experience what's called "telescoping." This term refers to the fact that substance-abuse trajectories in women tend to proceed faster than in men, so the addictive process from use to dependence unfolds on a faster timescale.[74]

Just as there are risk factors pulling people in the direction of cannabis use disorder, there are protective factors holding them back. A few of the relevant insulating factors (that were confirmed in part from our BARCS study) include being risk averse, having an awareness of family history of addiction (where people were cognizant of their increased risk and therefore took steps to avoid exposure), and being involved in occupational or athletic situations where substance use might impair performance. Other protective factors include initial negative experiences with the drug (especially feeling paranoid or anxious), fear of arrest, awareness of urine screening as part of their job requirements, religious beliefs, a strongly cohesive family background, and a general "meh" factor for cannabis. For the latter, students would tell us, "I tried the drug once, and it really didn't do it for me, so I never tried it again."

According to Yifrah Kaminer, a substance-abuse professor at the University of Connecticut Health Center, substance abuse of any sort in adolescence raises the odds that the individual will also have other psychiatric disorders, including conduct disorder (a young person's equivalent of impulsivity and acting out), major depression, or anxiety.[75] Conversely, the odds for alcohol and cannabis abuse are two to three times greater in those with diagnosed major depression. These syndromes co-occur for several reasons, including substance abuse as self-medication for psychiatric symptoms, as well as use of the drugs themselves causing the emergence of anxiety and depression symptoms. For example, cannabis in adolescence seems to cause short-lived mood increases, followed by more prolonged stretches of low mood.[76] But the point to be emphasized, Kaminer says, is that since substance abuse and psychiatric symptoms in teens co-occur, and both are multidimensional, then they require a multidimensional treatment plan.

More on structural and functional brain-imaging consequences of cannabis use

Because the human brain develops actively through adolescence until the 20s, and components of the ECS including CB_1 guide these events, consumption of cannabinoids risks disrupting those processes. Currently, almost 35% of American 10th graders report using cannabis.[77] Although rates of cannabis use among high schoolers remain constant for now, one worry is that they may increase if cannabis is legalized at a federal level.

So, what's the actual evidence that cannabis consumption is associated with structural brain changes? This is a more relevant question to ask, since functional brain alterations tend to be much more dynamic, perhaps fleeting, and only reflecting recent use. To summarize a much-debated topic, the structural evidence

is mixed but not impressive when it comes to demonstrating cannabis-related brain alterations. Recall that in our two-year freshman college-student BARCS study, we performed imaging on 450 of our students at baseline and followed up with as many of them as we could 24 months later for repeat imaging and IQ testing. We documented hard-to-miss alcohol effects. Heavier quantities and frequencies of alcohol consumption in our group were associated with significant shrinkage over time of the hippocampus on MRI and poorer two-year memory function. We failed to demonstrate any similar effects of cannabis on either brain or memory, however.[62] Barbara Weiland, at the University of Colorado Boulder, used very high-resolution MRI scans to compare several different measures of brain structure in 29 adult daily marijuana users (average age 27) and 50 adolescent daily users (average age just under 17). She compared each of these two groups to equal numbers of same-aged non-cannabis-using controls. Weiland found no significant structural brain differences between the marijuana users and controls for any of the key regions examined. Not only that, but the degree of separation between the two samples was minimal so that the size of the difference between the two groups hovered right around zero. As part of their study, the Colorado group also reexamined a dozen prior published papers that had undertaken similar measures, some of which had reported brain differences in cannabis users. They pointed out that the findings in these earlier papers were inconsistent. No two of them reported quite the same brain areas as affected. Some reported increases in structural volume, others decreases. In addition, the findings of many of the previous studies were complicated by the fact that the subjects were also alcohol users. As we and many others have shown, alcohol consumption has indisputable effects in shrinking brain structures. The Colorado study, unlike many prior efforts, matched subjects and controls very carefully on alcohol-use measures and also controlled for other possible complicating factors that could influence brain volume. These included tobacco use, age, sex, impulsivity, and depression.[78]

The same group of investigators then performed similar measurements in a group of older adults whose mean age was almost 70, who had smoked cannabis at least weekly for the past year, and on average had used it for close to 24 years. Cannabis users and non-users showed no differences in terms of total gray-matter or white-matter volumes when age and depression symptoms were taken into account. The users, however, had larger volumes in a handful of brain regions in parts of the frontal lobe, an area of visual cortex, and a region deep inside the brain concerned with motor movement and learning. The two groups also scored the same on a short computerized cognitive test. The overall conclusion was that once you control for age, cannabis use had no widespread effects on overall brain gray-matter volumes.[79]

So far then, the studies we've examined have not demonstrated any worrisome brain changes associated with even long-term cannabis use. The exception comes from the IMAGEN study of adolescents that follows a very large European population sample of 2,400 adolescents collected across many research sites. The design of the study is such that participants are followed multiple times as they

mature, with brain imaging and IQ testing, starting at an age well before alcohol and drug use begins. The investigators can therefore tell whether substance use alters the normal trajectory of structural or functional brain development during the teen years, without being confused by chicken-and-egg questions of whether the brain changes preceded substance use or vice versa. In one particular IMAGEN analysis, 46 boys and girls of 14 years of age who had used cannabis only once or twice were matched with others from the study who had never been exposed to THC. Completely unexpectedly, very large brain regions in both temporal lobes (which included the hippocampus and amygdala), the cerebellum, parts of the visual cortex, and the posterior cingulate cortex on both sides of the brain all had significantly greater gray-matter volume in the cannabis users. When the IMAGEN investigators went back to look at the previous MRI scans of these individuals, they could not explain these brain differences as a feature that had been there prior to cannabis smoking.[77] How did the investigators try and explain such an unlikely finding? One piece of the puzzle was that the areas where gray matter appeared to have increased after using cannabis corresponded closely both to maps of CB_1 cannabinoid receptors (which other investigators had created using PET scans) and to places in the brain where the CNR1 gene that codes for those receptors were switched on the most. The investigators looked very closely to see whether other factors such as personality differences or psychiatric symptoms might be responsible for the brain differences but found nothing. In addition, if cannabis kills brain cells, why did the adolescents who'd been exposed to it have more gray matter rather than less in their brains? One possible explanation is that cannabis has effects on slowing down normal pruning of neurons in the adolescent brain.

Long-term effects of cannabis use

What, if any, long-term effects occur from cannabis use is a hotly contested topic, as I'll explain. If you study brain-function tests, recruit a population of chronic cannabis users into a study, and test them on a series of cognitive and neurological assessments, you will undoubtedly find impairments. Many studies have shown this effect.[80] But key questions remain: if you can persuade your subjects to stop using cannabis, will all their test scores return to normal? And how long would you need to keep them away from the drug to make sure they had returned to baseline? A week, a month, or six months? This issue is a particular problem with cannabis, since the substance tends to persist in the body (and, critically, in the brain) for lengthy periods. Not only that, since many cannabis users also use other legal and illegal substances including alcohol that can affect thinking and memory, this concomitant use would have to be taken into account. Particularly so if the person continued to use these other drugs while abstinent from cannabis. Furthermore, most individuals (as we've seen) are not especially accurate in reporting their cannabis use. There are no standard units of recreational cannabis quantification. And the amounts and ratios of cannabinoids in the drug not only

vary from sample to sample but also have changed across time. Thus, compared to alcohol for example, it's hard to calculate an accurate relationship between the amount of drug someone has used over the long haul and any deficits you might detect. What's more, different researchers tend to use their own favorite scales and approaches to measure a particular cognitive domain such as memory, rather than all of them converging on a single best assessment method. Many of the existing studies were conducted predominantly in men. Finally, it's not entirely clear what the underlying brain mechanisms might be that are responsible for any persisting cognitive deficits.

Given all this imprecision, one creditable attempt to synthesize the large existing literature on this topic came from Samantha Broyd and her Australian colleagues.[80] The published papers consistently documented acute and chronic impairments across verbal learning and memory and to some extent working memory in cannabis users. Large impairments in attention and attentional bias had also appeared in many reports. Other common themes were acute deficits in psychomotor functioning and variable impairments in executive-functioning abilities (including inhibition, planning, reasoning, interference control, and problem-solving). When Broyd and colleagues examined the persistence of these problems following abstinence, many of the above chronic deficits tended to melt away. Those that diminished to a "plus-minus" (meaning, maybe present) level included problems in verbal learning, memory, and attention. Difficulties in executive functioning such as planning and problem-solving didn't shift much over time with quitting. These were not markedly impaired in chronic users, however, even prior to abstinence from cannabis. The researchers concluded there were likely persistent effects on attention and psychomotor function and possible persisting effects on verbal learning and memory after abstinence. They admitted, however, that this whole question of recovery of function after prolonged abstinence is murky, particularly since the vast majority of studies they surveyed didn't follow the subjects beyond about a month. Given the fat-soluble nature of cannabis, ideally one would continue testing subjects significantly beyond that time. Broyd also drew attention to the fact that more recent studies suggest impairment in verbal learning and memory may indeed recover with prolonged abstinence. One very large prospective study tracked young-adult research volunteers across three periods of data collection spaced four years apart. Compared to individuals who continued heavy cannabis use, former heavy users who abstained from cannabis for a year improved cognitively on tests of immediate verbal memory. Furthermore, these long-term abstinent subjects did not differ from comparable individuals not using cannabis, on any cognitive measure.[81] A second study, however, detected impaired attention even after two years of abstinence.[82] The very fact that review papers in this section dance around a "maybe yes, maybe no" and "yes, but" set of conclusions suggests to me that, while cannabis-related cognitive problems may exist, they are subtle and likely to fade over time with continued abstinence.

The extent to which cannabis is damaging to cognition remains full of

contradictions and unanswered questions. Whether the proportions of CBD, minor cannabinoids, and terpenes in cannabis have any long-term cognitive effects is completely unexplored. Although there are many suspicions that an early age of starting cannabis use and heavy use in adolescence may be most damaging to cognition, these are also understudied topics. One advance that will shed light on this is the Adolescent Brain Cognitive Development (ABCD) Study initiated by the National Institutes of Health.[83] This effort has begun to follow eleven thousand youngsters recruited from across the United States beginning at age 10, prior to when most individuals begin substance use. The study tracks these volunteers through their teens at least annually with detailed cognitive tests, MRI scans, and investigations of their families, life events, and substance use. Large-scale studies such as these have the potential to address many key questions in the field (which we alluded to earlier in discussing the IMAGEN results). These include clarifying the what-caused-what problems, whether brain changes associated with substance use preceded or followed engaging with the drug, and whether normal brain developmental patterns are thrown off course by substance use of different sorts.

A major set of questions surrounds general health risks associated with cannabis use. A useful review from Germany attempted to synthesize information on this topic.[84] Here is a brief summary. Chronic cannabis use can cause bronchitis and chronic cough. But unlike tobacco smoking, there is no apparent link to either lung cancer or throat cancer. Risks for these disorders are probably increased in people who smoke cannabis and tobacco together (spliffs, blunts, and so on), but there seem to be few hard statistics available on this latter question. It's also likely that consuming cannabis through smoking rather than vaporizing is accompanied by particular risks due to inhalation of combustion products. On the other hand, there was a temporary outbreak of a sometimes-severe respiratory illness several years ago, caused by the addition of inexpensive carrier material to THC vape cartridges that proved toxic when heated. In discussing the ECS, I mentioned that cannabinoids may have adverse effects on liver healing; there is some evidence they can worsen the fatty liver and liver scarring that is part of hepatitis C. Some chronic heavy cannabis users experience repeated episodes of severe nausea and vomiting, the rather rare so-called cannabis hyperemesis syndrome, which is relieved temporarily by very hot showers. Why this intervention works isn't known. Anyone who's ever used cannabis is aware that it speeds up heart rate. There are rare cases of heart rhythm problems being provoked by use of the drug, as well as very uncommon cases of heart attacks. Many of these cases have occurred in individuals who had preexisting heart disease. To put all of this in perspective, however, compared to the health harms attributable to alcohol or tobacco, those due to cannabis appear to be much less dire. Harmfulness is an important issue we will plunge into in some detail later in this chapter. Over the next couple of decades, we will undoubtedly learn more about possible chronic health effects associated with cannabis consumption, particularly as both THC concentrations and the number of marijuana users rise.

Long-term effects in older adults of youthful cannabis use

Following a research cohort for two years to look at longer-term effects of cannabis use (as we did in BARCS) is one thing, but how about measuring the current consequences of the cannabis somebody smoked 50 years ago? Susan Bookheimer, a UCLA neuroscientist, and her collaborators recently performed a study whose implications might strike fear into the hearts of many of the people who lived through the ’60s and are still walking the earth.[85] They say that if you can remember the ’60s, you weren’t there. But let’s suppose you *were* there in the 1960s and ’70s (when cannabis use doubled), you *did* inhale, and you are now perhaps contemplating retirement. Like many in your age group, you may be concerned about the possibility of Alzheimer’s disease. Given your ’60s weed use, should you be extra-worried concerning your brain? In other words, you might not remember the ’60s, but can you remember where you left your keys five minutes ago?

To address these questions, Bookheimer recruited her 57- to 75-year-old subjects from the local community and screened out anybody who’d used recreational drugs other than cannabis more than once, ever. She focused in on 24 individuals who’d begun using cannabis before age 20, had smoked it at least 20 days per month in at least one calendar year, and had pretty much quit using by age 35. On average her subjects had begun using marijuana at age 17, used for 11 years, and been abstinent for 30 years. None were heavy drinkers. She also recruited an equal number of individuals who said they had never used cannabis or any other illicit substance, ever. All subjects had a physical exam to ensure they were healthy and a urine screen to rule out anyone currently using recreational drugs. Everyone completed a battery of cognitive tests (focused especially on memory), followed by a research-quality MRI scan, where the research subjects had super-high-resolution structural images taken of their hippocampus. Compared to the group that had never inhaled, the former cannabis smokers had around 10%–15% smaller gray-matter volumes, specifically in several hippocampal subregions. Such reductions were not seen in other nearby brain regions also measured during the scan. Although there were no significant cognitive-test differences between the two groups, the former cannabis tokers tended to score lower in every test.

What are we to make of these findings? Significant cannabis use in early life seems to have persisting effects on brain anatomy, at least in the hippocampus, several decades after these individuals had quit using the drug. Inevitably, there are some problems with the study design. The number of subjects examined was small. Participants were being asked to recall their drug use 40–50 years in the past, which is challenging at best, particularly so for a drug that affects memory. Finally, there is a chicken-and-egg problem in that we don’t know the volume of these subjects’ hippocampuses (strictly termed “hippocampi”) before their first cannabis use (or nonuse in the case of controls). And although unlikely, perhaps people with small hippocampi are more prone to smoke cannabis. (The ABCD Study will actually answer that question.) But despite these caveats, the study

certainly raises concerns. For one thing, the likelihood is that these brain changes were due to the THC in cannabis. Because current chemovars have a much higher percentage of that substance than 50 or 60 years ago, they thus may be potentially more harmful than the relatively weak "grass" of the '60s with its 4% THC, chockablock with stems and seeds. Second, the earliest brain changes of Alzheimer's disease attack these same hippocampal areas and their surrounding gray matter very specifically, so those at risk for the disorder may have diminished resilience to its effects, if they're unlucky enough to develop it. These speculations don't have answers at this point, and I certainly don't want to be a scaremonger, because the evidence doesn't warrant that. But this is clearly one of those provocative scientific studies that deserves to be rerun in a much larger sample to see whether the results hold up. If they do, that would be concerning. Although on the other hand, recent small-scale studies in Israel hint that cannabis is a useful treatment for agitation and "sundowning" in elderly demented patients.[86] So if youthful cannabis use hastened your late-life dementia, we may know how to take the edge off your symptoms.

A related issue concerns the increasing numbers of older individuals who use cannabis, either recreationally ("It's legal now!") or to ease their arthritis pain and to help them sleep better at night. Such use raises a host of questions. Are there risks to using cannabis in later life? If so, what are they specifically? Dose for dose, do elders metabolize and process cannabis constituents differently than young folk so that they need to adjust THC quantities? Do older brains respond differently to cannabinoids than younger ones? This entire topic is essentially unexplored. But all the above questions are important to answer, for obvious reasons.

Pregnancy effects

We've already noted that perception of cannabis's potential harms is on the decrease. Perception of harm deters use. Pregnant women are now more likely to use cannabis as a natural substitute for medications prescribed for anxiety and depression as well as morning sickness.[87] Letting any kind of substance that isn't supposed to be there into the developing fetal brain and body is a potential risk. We know that recreational substances such as alcohol and nicotine, as well as some physician-prescribed medications such as thalidomide, can reach the fetus via the placenta and the umbilical cord to interfere with fetal development. Risks associated with various recreational drugs include premature births, birth defects, low birth weight, fetal alcohol spectrum disorders, and miscarriages. We've also learned that cannabinoids, being very fat-soluble, concentrate in the nervous system as well as breast milk, and that anandamide and CB_1 receptors guide both fetal implantation and critical aspects of human brain development. So, how do we determine risk information related to maternal cannabis consumption during pregnancy, and should we be concerned? Well, marijuana is the most common illicit drug used during pregnancy, particularly by teens. It may exert different

effects across the three trimesters of pregnancy. A survey of over fourteen thousand pregnant women[88] found past-month cannabis use of about 4% during pregnancy. The rates were highest at over 6% in the first trimester. Use was doubled (at 14%) in 12- to 17-year-olds and greater in non-Hispanic Black women. Another recent study from Northern California surveyed over a quarter of a million women enrolled in the Kaiser Permanente health system. Between the beginning of 2009 and the end of 2017, self-reports of daily, weekly, and monthly cannabis use among women in the year before pregnancy almost doubled. Rates of use during pregnancy itself increased from almost 2% to 3.4% over the course of the study.[87]

Because these numbers are nontrivial, it's important to pin down whether there are any major adverse effects on babies born to cannabis-using mothers, either acutely or long-term. There certainly are identifiable problems in rats and mice born to rodent moms exposed to THC during pregnancy. But such findings are not always a reliable guide to what happens in humans. So currently a number of studies of pregnant women are underway to address those questions. There are some preliminary data to consider. Women in the Maternal Health Practices and Child Development Project who smoked cannabis during pregnancy gave birth to infants who by 10 years of age had significantly higher depression rating scores than those children of otherwise comparable nonexposed women.[89] An additional worry is that because of its fat solubility, THC is concentrated in breast milk and passed along to infants if their mothers use marijuana.[90] So the concern is not limited to cannabis exposure during pregnancy but also in the first year of life in breastfed babies.

What is the quality of advice that pregnant women are being provided regarding cannabis? In a now-infamous investigation, Betsy Dickson and coworkers[91] designed a study where the investigators called four hundred dispensaries in Colorado and claimed to be eight weeks pregnant and experiencing morning sickness. "What would you recommend I do?" they asked. Over two-thirds of the locations called advised treatment of the claimed morning sickness with cannabis products. Medical dispensaries (at 83%) were particularly liable to provide this recommendation, with the majority of staff basing their advice on personal opinion. Overall, 36% of dispensaries stated that cannabis use is safe during pregnancy. While most advised discussion with a healthcare provider regarding cannabis use, fewer than one-third of them made this recommendation without prompting.

Concern is appropriate but must be balanced with knowledge of actual risks. For example, developmental consequences of some recreational drugs on fetuses have been overblown. Recall the dire warnings in the 1980s regarding the coming epidemic of vast numbers of mentally challenged, behaviorally abnormal, "doomed from the womb" "crack babies," for example. The supposed scourge never truly materialized.[92] Similar cannabis scaremongering is already appearing —take for example the November 23, 2018, British *Daily Mail* headline, "Could medical cannabis be the new THALIDOMIDE? Fears of a crisis as doctors

consider doling marijuana-based medicines out to pregnant mothers despite evidence the drug can damage foetuses." [93] While cannabis-related experiments on pregnant laboratory rodents are relatively straightforward to conduct, rats are not humans (no matter what you might think regarding your surly coworker or local politician), so as mentioned above, results from animal studies are not directly transferable into the human realm. For example, neurogenesis in the fetal prefrontal cortex takes a full five months to complete in humans, versus one week in mice. Other precautionary issues are that cannabis may be consumed along with tobacco (in "spliffs" and "blunts"), and contaminants such as pesticides or heavy metals can be found in cannabis that may themselves be independently toxic to fetuses.

A useful comprehensive review of consequences of human prenatal marijuana exposure in relation to later development of neuropsychiatric problems[94] pulls together disparate information from laboratory animal and human-cohort studies. The authors conclude that in rats, THC reorganizes the DA system in brain regions concerned with mood and conscious behaviors. CB_1 receptors in human fetuses have distinctly different distribution from those found in the adult human brain. For example, in midpregnancy there is a spike in CB_1 receptor concentrations in the amygdala and hippocampus. In animals, THC exposure interferes with the development of other brain neurotransmitter systems including DA and opioid circuits. Although increased risk for schizophrenia in adolescence is a theoretical concern down the road for cannabis-exposed fetuses, the sort of large-scale epidemiologic studies to show such a relationship have yet to be performed. Bottom line: there may well be risks associated with cannabis use in pregnancy, but their nature, magnitude, and frequency are yet to be determined.[95] This lack of actual information hasn't stopped some scaremongers in the medical world from making dire predictions. Stuart Reece in Australia, for example,[96] uses particularly alarmist language: "massive scale chromosomal shattering or pulverization can occur . . . aggressive onset of addiction-related carcinogenesis . . . downstream genotoxic events including oncogene induction and tumor suppressor silencing. . . . [THC] in this respect is similar to the serious major human mutagen thalidomide." Paul Merlob in Israel reviewed the evidence for cannabis use during pregnancy affecting the fetus and newborn with regard to issues of fetal growth, stillbirth rates, preterm births, congenital malformations, and neurobehavioral alterations in newborns. Once potential confounders such as use of tobacco, alcohol, and other recreational drugs had been accounted for, existing studies were either inconclusive or found no marked effects. "Most published studies report inconsistent results. . . . Well-designed studies are needed which should take into account all confounding factors for different neonatal outcomes while accurately measuring quantity and timing of exposure to marijuana." [97]

My personal opinion? Don't tempt fate. Until we have a better handle on risks, why subject your unborn baby or newborn to possible health problems?

How dangerous is cannabis overall as a recreational substance?

And how do its risks compare to those of other recreational substances?

How do we summarize the adverse health effects of recreational cannabis use and quantify the size of the substance's overall risks? More generally, is there any way to rationally compare the harms and risks of using a particular substance compared to other substances? Or, more specifically, how harmful is using cannabis compared to drinking alcohol or coffee, or smoking tobacco cigarettes? These are questions debated by lawmakers and public-policy analysts, among others, but it's appropriate to pose them here. Part of the problem in addressing these issues is that they are located at an uncomfortable interface between science and politics.[98] Politicians are often elected on promises to reduce drug use and crime. Nixon was a prime example. Admitting that any illicit recreational drug is less harmful than generally supposed will not help their odds of reelection. An illustration of the political-hot-potato status of drug-harm-related issues comes from David Nutt. One of the more articulate voices in this debate, Nutt, a professor of psychopharmacology at Imperial College London, presented evidence that alcohol was more dangerous than many illegal drugs, including cannabis. For his honesty, in 2009 Nutt was consequently fired from his role as long-time chairman of the UK government's Advisory Council on the Misuse of Drugs.[99] But as Nutt says, "Being willing to change our minds in the light of new evidence is essential to rational policy-making." [100] Certainly, having the relative risks of recreational drugs quantified by scientists and drug experts rather than politicians seems rational.[98,100]

How to think about drug-related harm? At first blush, if I decide to take a few Valiums to help me get through the day or a shot or two of vodka as an eye-opener before I go to work, that could strictly be my personal choice. But if I'm employed as a school-bus driver, missile-silo officer, steel-mill blast-furnace operator, or neurosurgeon, then showing up for work mildly intoxicated can impact other individuals adversely. Also, if I snort cocaine on the weekend in a way that doesn't measurably affect my work performance, am I nevertheless helping a local criminal drug syndicate or ultimately the Sinaloa cartel in Mexico? If one substance such as alcohol is rated as generally more harmful than another such as cannabis—but is legal—how is that fact weighed into the harm equation? Such questions were first raised almost 50 years ago by Samuel Irwin, a professor at the University of Oregon. Then, beginning in 2007, Nutt and his colleagues came up with a rational starting point for ranking recreational substances (both legal and illegal) relative to each other. This scheme is laid out in several papers [99,101,102] and summarized in Nutt's book.[100] This group considered the large and diverse means by which drugs can lead directly and indirectly to harmful consequences, and ultimately how to weight each such classification to allow comparison across substances. These investigators proposed two major categories had to be considered: harms to the users themselves (for example, toxicity or loss of relationships) and harms to others (for example, crime and economic costs) both to

individuals and at a population level. Harms to the users themselves comprised nine subcategories, and harms to others a further seven. I will try to summarize this somewhat-complicated classification here, because it is thorough and comprehensive and relevant. I also acknowledge the thoughtfulness and hard work that resulted in its creation.

The first major item in the category of harms to the user was *drug-specific mortality*, defined as instances of direct harm to individuals using the drug. An obvious example is deaths from poisoning. This can be gauged by comparing the amount needed to produce psychoactive effects with the fatal dose, to give a safety ratio. For alcohol, this number is 10. If 2 units (2 beers, 2 glasses of wine) cause intoxication, then 20 units will kill you. Although the uptick in alcohol-related deaths has been partially obscured by the opioid epidemic, the number of deaths attributable to alcohol in the United States increased 35% between 2007 and 2017. In particular, deaths among women rose 67%.[103]

So, when it comes to drug-specific mortality, cannabis is clearly safer than both alcohol and opioids because, although huge doses may push you into an extremely unpleasant delirious state, there are virtually no fatalities. Perhaps none at all. This, as we've seen is true in part because CB_1 receptors are not located in parts of the brainstem that control breathing and heartbeat. *Drug-related mortality*, on the other hand, counts deaths from chronic illnesses, for example, suicide, alcoholic cirrhosis, tobacco-caused lung cancer, and fatal traffic accidents. As discussed earlier, cannabis is much less harmful than alcohol when it comes to intoxicated driving but not risk-free, given the slightly elevated crash odds reviewed in the Swedish meta-analysis study. The category of *drug-specific damage* includes physical harm short of death due to a drug. The sort of items included here would be holes in your nasal septum due to cocaine use; chronic bronchitis, heart attack, or COPD from tobacco; and chronic liver disease from alcohol. Again, cannabis scores relatively low in this category, unless we count individuals who smoke cannabis mixed with tobacco, as is common in both the Netherlands and Jamaica. But that damage results from the tobacco and not the cannabis.

Let's pause for a second to look at some of the alcohol-related statistics of the sort we encountered in the realm of marijuana in Chapter 6. George Koob, the director of the NIAAA, quotes some statistics for alcohol damage in the United States that illustrate the magnitude of alcohol damage in these categories. In the United States annually, 179 million people, or 66% of the adult population, use alcohol. Moreover, 5.3% of the population, or 14.5 million people, are diagnosed with an alcohol use disorder. Overall, 88,000 people die from alcohol-related causes of all sorts, with nearly 50,000 of them from acute events including overdoses or injuries, and another 39,000 people from chronic causes such as cirrhosis and cancers. In addition, 50% of all liver-disease deaths are due to alcohol. There have been significant increases in binge drinking over the past 10 years that are driving higher rates of emergency-room and hospital visits; and 5.7% of the population, or 14.1 million people aged 18 and over, meet criteria for an alcohol use disorder. Extreme binge drinking, where users consume huge

amounts of alcohol in a short span of time, is also on the increase.[104–106] In comparison, 4.2% of the population misuses opioids; and 0.8% of the population, or just over 2 million people, have an opioid use disorder. There are 47,600 deaths by opioid overdose annually; 15% of these involved alcohol in 2017. Stacked up against these numbers, the statistics for cannabis barely make a dent in this category of drug-specific damage.

The area of *drug-related damage* captures general harm short of death from drug-related activities and behaviors—for example, acquiring HIV from needle use of IV-administered drugs, nonfatal DWIs, and workplace accidents such as falling off a ladder when drunk or stoned. Cannabis scores modestly on this item. Dependence and addiction rates are relatively high for tobacco and for alcohol. As we saw earlier, the overall dependence rate for cannabis use is about 9%—so, significant. *Drug-specific impairment of mental functioning* includes examples such as drug-impaired judgment lapses leading to unprotected sex or deciding to drive drunk. This category is hard to quantify, but alcohol and cocaine are clearly more harmful than cannabis. Likely due to psychosis risk, delirium, and amotivation, Nutt and colleagues scored cannabis detectably in both this and the next category. *Drug-related impairment of mental functioning* subsumes features such as late-life alcohol-related dementia, mood disorders secondary to the drug or its associated lifestyle, loss of pleasure and interest in everyday activities, nonspecific depressed mood, and memory loss. *Loss of tangibles* is a slippery category. In part it depends on whether legal penalties exist for a particular drug. Currently, recreational marijuana is still illegal in many US states, but alcohol in none, for example. Being incarcerated because of possession of a small amount of marijuana is something that can be remedied by changing laws on drug possession, but deciding to spend large amounts of money on cannabis rather than saving for a house would also fall into the category, as would losing your house due to drug use or if it were seized by the authorities as part of a legal penalty. The final category of harms to users is *loss of relationships*: for example, when John's significant other left him due to his persistent cannabis use, or when partners exit a relationship related to the user's violent behavior when intoxicated. This category is many times more problematic for alcohol than it is for cannabis, Alex Berenson to the contrary.[107]

The second major group of issues defined by Nutt and his collaborators was that of harm to others, considered at the individual and population level. The first item under this heading is *injury*, which includes both events that were accidental in nature, such as being run over by an intoxicated driver, and injury that was intentionally inflicted, such as being shot when inadvertently approaching a concealed illegal cannabis growery in a national park. Other examples include being a domestic-violence victim or fetus damaged by drugs. Alcohol is far more dangerous than cannabis in this regard.[108] *Crime* is illustrated by consequences of theft to support one's drug habit, growth of drug gangs, or vandalism when intoxicated. Drug laws obviously have a strong impact on this category. For example, in the United States during alcohol prohibition in the 1920s, booze

smuggling and speakeasies were tied into the criminal activity of manufacturing and distributing an illegal substance. With the repeal of prohibition, this problem disappeared. *Economic cost* subsumes such instances as lost workdays due to intoxication or withdrawal, and costs of drug-related health impairment. Here, cannabis was rated above cocaine, crack, and amphetamines, although dwarfed by scores of alcohol and tobacco. *Impact on family life* includes such examples as neglect of a significant other and family, drug-related violence, and absence due to incarceration on drug-related charges. Cannabis scored modestly here. *International damage* captures such events as fallout from the war on drugs—for example, being threatened or harmed by a drug cartel. This is another legal or political category. *Environmental damage* includes issues such as illegally diverting streams to supply illicit cannabis cultivation, use of harmful fertilizers or pesticides on illegal drug crops, and generating toxic waste from a methamphetamine "cooking" operation. Nutt uses the examples of discarded needles and broken bottles, and aggressive behavior outside bars. *Community decline* includes such things as drive-by shootings related to turf wars between drug dealers, crack houses, and drug shooting galleries.

Nutt and colleagues developed an algorithm to decide how all these 16 different criteria should be differentially weighted, which they termed "multi-criteria decision analysis." [102] Nutt convened an expert panel to score 20 commonly used recreational drugs classified into four very broad groups: stimulants, depressants (which somewhat awkwardly included cannabis alongside alcohol, benzodiazepines, ketamine, and GHB), opioids, and empathogens/psychedelics (ecstasy, LSD, and mushrooms). The panel rated each of the 20 drugs from 0 (indicating no harm) to 100 (designating most harm) in each category from across all the earlier-mentioned 16 criteria. The panel's final summary scores for some of the drugs, ranked in order of harmfulness, were 72 for alcohol, 55 for heroin, 54 for crack cocaine, 35 for methamphetamine, 27 for powder cocaine, 26 for tobacco, 20 for cannabis, 15 for benzodiazepines such as Valium and Xanax, 9 for ecstasy, 7 for LSD, and 6 for psilocybin mushrooms. For alcohol, harm to others was scored at about double the amount of harm to the user; for cannabis, this relationship appeared to be reversed. Examining the raw scores for harm to others and harm to users respectively, alcohol scores a whopping 85 and 55, whereas cannabis scores a 15 and 25. Some of the panel's considerations require explanation or seem counterintuitive initially. Tobacco may be very harmful in the long term but not in the short-term; and outside of evading tax laws on cigarettes, for example, related criminal activity is low. On Nutt's algorithm-based score, cannabis gained many of its points from rankings of both drug-specific and drug-related impairment of mental functioning, "mostly because of the harms associated with smoking, and the drug's links with depression and psychotic symptoms," as well as the development of dependence in around 10% of users.[100] The panel usefully made explicit in their paper [102] not only the separate contribution to the overall scores of harms to users and to others but each separate ranking for each substance of the 16 subcategories, so it's possible to parse their decisions fairly

transparently. Subsequently, the European Union adopted the same approach to create a very similar ranking.[109] The weightings appear slightly different from the earlier British paper in that the relative proportion of harm to others for cannabis seems to be significantly diminished.

Ranking harms using this sort of approach is rational in terms of considerations that must be weighed by individuals forging policy in the realm of law enforcement, social-care strategies, and healthcare. Some of the criticisms that have been leveled against this perspective were raised by the authors themselves, including the fact that they scored only harms and not benefits (for example, the utility of medical cannabis). They also did not include tax revenues and employment generated by legal drug sales. For example, if recreational cannabis were legalized federally, and these criteria were included, the balance would shift significantly in a positive direction. At some point, enforcement of laws prohibiting a substance may be doing more harm than the drug, a notion that in some ways influenced the repeal of alcohol prohibition in the United States. Many people would argue that a parallel situation exists currently for cannabis.

More generally, the authors did not fully weight the role of a drug's availability and legal status. Ultimately, it's also impossible to avoid subjective value judgments with regard to the weights placed on different types of harm.[98] Others have criticized Nutt and colleagues for not properly taking prevalence of use into account. The panel tried to consider how many people actually used a drug, as a way of assessing its overall impact. For example, if many people use drug A, which is moderately harmful, that fact has to be weighed against the much smaller number of people who use drug B, which is extremely harmful. This quantification turns out to be difficult to implement in practice, as has been pointed out.[110]

This has been a long chapter, necessarily so, because cannabis toxicology is an important and complex topic. As one of the first substances used recreationally, precisely because of its psychoactive effects, it's hardly surprising that psychological problems such as psychosis and delirium tag along in its wake. But as a reminder of the complexity of the plant's chemical makeup, it's not entirely unexpected that cannabis also contains a potential treatment for psychosis. Against conventional wisdom, it's now clear that cannabis dependency is a real phenomenon and not just a "psychological" issue. Adolescent cannabis use seems to be associated with reversible cognitive problems, as discussed previously. Also, the drug may possibly cause structural brain changes, but overall the evidence for this seems rather weak. Effects on the developing fetus and infant when mothers use cannabis during pregnancy or while breastfeeding are underexplored, but these practices seem risky and ill advised. Research regarding age-related issues is currently almost nonexistent, despite the large and growing population of older cannabis users. I concluded this chapter by trying to gauge the dangerousness of cannabis compared to other recreational substances such as alcohol, tobacco, and opioids in terms of the direct and indirect harms that cannabis causes. It is not a benign drug, primarily because of its tendency to increase risk for psychosis (and

possibly other mental-health issues) and secondarily through its effects on driving ability. Since our neighbor to the north has already taken the plunge in terms of legalizing recreational cannabis, the significant social experiment underway there is being closely watched and will inevitably provide much useful information on cannabis-related toxicity (as well as benefits) over the next few years.

Chapter 8

CHEMISTRY, CHEMICAL ANALYSIS, AND EXTRACTION

Terpenes to Tinctures

> Israel is a crossroads for smugglers . . . who get Lebanese hashish from Jordan through the Negev & Sinai deserts to Egypt. Hence the police vaults are full of material waiting for a chemist.
>
> RAPHAEL MECHOULAM, "Marihuana Chemistry," 1970[1]

In this chapter, we'll look at the following questions: What are chemovars and terpenes? What are cannabis concentrates such as BHO, dabs, and shatter, and how are they made? Why and how do people use them? What are the risks associated with them?

Chemovars

In Chapter 3, we discussed how cannabis breeders develop different varieties to intensify the plant's key chemical characteristics such as concentrations of THC, terpenes, or CBD. What is the best way to classify those varieties? An intuitive approach is to bypass botanical descriptions and go straight to chemistry as the bottom line. After all, the plant molecules that produce the particular type of high, specific medicinal effect, or pleasant smell and taste are why we are interested in a product. The essential question is what relevant chemicals, and in what amounts and proportions, are found in a given cannabis plant? Providing these details would be the equivalent of listing key ingredients in foods. In that case, you want to know what you are about to consume in terms of calories, salt, preservatives, and carbohydrates. Similarly, for cannabis, quantifying ingredients provides useful information beyond the fact that the bud you are contemplating is some purported indica variety that looks prettily plump, resinous, and smells like lemon and strawberry. Currently, such important ingredient information is missing from many dispensary products. And any information that is there may well be inaccurate. This bottom-line, objective, list-the-contents approach leads directly to the concept of "chemovars," a contraction of "chemical varieties."

A little earlier, we discussed using chemical varieties as a direct way to distinguish one type of cannabis plant from another. This approach originates with Robert Connell Clarke's 1993 book, *Marijuana Botany*,[2] and was brought to full

fruition by Mark Lewis and Ethan Russo.[3] It involves analyzing and displaying the contents of any cannabis variety in an easily understood graphical format. This checklist includes the species (for example, sativa dominant), class, type (for example, flower, resin), and percentages of principal phytocannabinoids (for example, THC, THCA, CBGA, CBD, etc.) and of terpenoids (for example, myrcene, limonene, pinene, etc.—compounds that we will have much more to say about later). In addition, the list includes the predominant scents and tastes (for example, fruity, citrusy, floral, earthy), and subjective therapeutic or entourage effects (for example, relaxation, focus, comfort, energy, calm). Lewis and his coauthors are in the process of patenting their graphical display system under the name PhytoFacts.[4] They plan for this intuitively clear approach to be used both by researchers and as a standard display method in dispensaries. The foundational investigations on which this method is based[5] posed a series of practical questions. Some examples: if you want to develop a "phytoprint," a unique fingerprint or profile to characterize cannabis specimens, what sort of equipment do you need, and how do you standardize the assay procedures? What kind of internal standards (stock chemical reference specimens) should you use as the gold standard to compare the same assays across different sites? Once you develop the assays, how repeatable are they? If you repeat the same measurement five times in a day, or daily for five days, do all the values agree with one another or bounce around randomly? Matthew Giese and his collaborators were able to address all these questions satisfactorily and to show that their methods yielded stable and repeatable answers. Once you have settled on a solid method that replicates over time, then you can address a whole series of new questions. These include tracking what happens when you profile different samples of purportedly the same variety from one growery; how similar are they to one another? Or even how do values vary from different parts of the same individual plant? How about samples of a particular variety from a dispensary in Denver compared to samples in San Francisco? Or Girl Scout Cookies buds sold at the same dispensary six months apart? The chemovar approach to assaying terpenes is also important because it ultimately allows researchers to address the frustratingly underexamined claims regarding entourage effects. Once you are able to quantify all the ingredients in the "recipe" of a particular cannabis variety, then some of the elusive claims made about synergism of different cannabinoids and terpenes will be fully testable.

This is the promise of the chemovar approach to key ingredients. It does seem to offer a reliable method to compare apples to apples (or at least buds to buds) across different laboratories. But until there is some sort of state- or federally mandated approach to cannabis fingerprinting, different dispensaries are free to use any assay laboratory and method they choose, or none at all. What is also extremely important to know but is not often addressed is the presence of contaminants within the sample. Assaying for fungi, heavy metals, pesticides, and bacteria calls for a completely different set of procedures. Currently, all these assay procedures are loosely regulated (or not regulated at all) at a local level and are crying out for standardized, uniform federal rules so that cannabis users

anywhere can be confident that what they are purchasing is not likely to harm them.

If I just persuaded you that chemovars represent the final word on state-of-the-art science-based cannabis classification, you'll be happy to learn a group of researchers at Washington State University just moved this process a significant step farther down the road.[6] They accomplished this by looking not only at the chemical composition of cannabis-plant material but by linking this information to measures of expression of the genes that synthesize the plant's key chemicals. The group, led by B. Markus Lange, did not come up with a catchy title for their approach, so as a default let's term it "geno-chemovars." Previous analyses have shown that as one would expect, drug marijuana and nondrug hemp differ in their ability to synthesize cannabinoids. Marijuana has a specialized form of the gene that makes THC (known technically as the "tetrahydrocannabinolic acid synthase allele"), and hemp typically has instead a different variant of the gene specialized in making CBD (known as the "cannabidiolic acid synthase allele"). Other scientists performed RNA analyses of female flowers to determine how switched on these forms of the gene are (technically termed "transcriptome analysis") in drug cannabis compared to hemp. As expected, THC cannabinoid pathway genes were significantly ramped up in drug varieties.

Analogously, once the genes that are responsible for the manufacture of terpenes are switched on, they too make corresponding RNA copies of themselves, which then direct the cell in manufacturing those molecules. With his collaborators, Lange extracted RNA from different cannabis strains by abrading trichomes with tiny glass beads, perhaps inspired by Herman Hesse. This scrunchy erosion process ruptured the plant-cell walls, releasing the plant-cell contents. The resulting RNA was sequenced, and the related switched-on genes specifically identified. Then the various networks of genes contributing to individual patterns of cannabinoid and terpene production could be pinpointed in different cannabis varieties. This über-scientific procedure leads to a complex but highly specific ID of a cannabis variety, defined both by its genetic and chemical profile. I would compare the strategies to the difference between the FBI having your fingerprints and photo on file (chemovar) versus also having a sample of your DNA (geno-chemovar).

Having powerful genetic tools at our disposal enables scientists to ask interesting and hitherto un-addressable weed-related questions. A pioneering 2015 genetic study set out to address a bunch of fundamental cannabis issues. It ended up shattering many preconceptions.[7] Sean Myles and his Canadian colleagues looked at DNA derived from over 40 hemp samples and more than 81 drug-cannabis samples. The investigators were full of questions. What is the underlying genetic structure of all plants from the genus *Cannabis*? Are hemp and drug-type marijuana genetically distinct? Are indica and sativa genetically close relatives or distant ones?

SNPs in DNA are a major source of person-to-person and plant-to-plant variation. These SNPs (single nucleotide polymorphisms, which we encountered

earlier in the Dunedin study) show up in cannabis DNA as often as 1 in 100 DNA base pairs. That translates into there being plenty of genetic variation in cannabis. What were some of Myles's team's major findings? First, in a shocking buzzkill to the wisdom of budtenders everywhere, there was no obvious DNA fingerprint that parsed *C. sativa* from *C. indica*. Second, correlation between the genetic structure of cannabis varieties and their reported ancestry was modest to weak. Official labels such as Hindu Kush were clearly based more on breeders' whim than geographic origin. Third, prior to the Canadian study, scientists had assumed that cannabis varieties used for fiber and seed production derived from *C. sativa*. But the genetic results in this study were completely incompatible with that hypothesis. Hemp was genetically more similar to *C. indica* type marijuana than to *C. sativa* strains. In fact, a strain's genetic distance to hemp was negatively correlated with its reported *C. sativa* distance. A paragraph or two back, we chatted about cannabinoid expression in hemp versus marijuana. The Canadian scientists showed that the DNA differences between drug cannabis and hemp were not simply restricted to genes involved in cannabinoid production. They were far more fundamental and widely distributed across the entire cannabis genome.

Another myth busted by the study was that cannabis "strain" names delineate very specific distinct chemovars. Instead, the genetics research group showed that these names do not reflect a meaningful genetic identity. In some cases, the assignment of indica versus sativa ancestry disagreed wildly with genotype data. For example, Jamaican Lamb's Bread (reported as 100% sativa) was 98% identical to a reported 100% indica strain from Afghanistan. Thus, budtenders are likely inadvertently passing along highly inaccurate descriptive information that they have received from equally uninformed cannabis breeders. In over a third of these researchers' comparisons, "samples were more genetically similar to samples with different names than to samples with identical names." The researchers stated that "inaccuracy of reported ancestry in marijuana likely stems from the predominantly clandestine nature of cannabis growing and breeding over the past century. . . . Recognizing this, cannabis strains sold for medical use are often referred to as sativa or indica 'dominant' to describe their morphological characteristics and therapeutic effects. Our results suggest that the reported ancestry of some of the most common marijuana strains only partially captures their true ancestry. . . . We conclude that the genetic identity of a marijuana strain cannot be reliably inferred by its name or by its reported ancestry." [7] Certainly one way to think about that information is to understand it reinforces a bottom-line-chemovar or geno-chemovar approach—a "just tell me what's in there" strategy—rather than relying on a fanciful, potentially misleading dispensary description.

The last, truly interesting, important finding from Myles and his scientific collaborators was that levels of genetic diversity were significantly greater in hemp than in recreational and medicinal cannabis. This suggested to the researchers that hemp cultivars come from a much broader genetic base than those of drug strains. Of course, another possibility is that marijuana, like lineages of Egyptian pharaohs or Habsburg monarchs, is characterized by inbreeding among

close relatives. These two possibilities are not mutually exclusive. The bottom line here is that *Cannabis sativa* and *indica* may represent clusters of genetic diversity, where one can be parsed from the other up to a point using DNA analysis strategies, but that extensive crossbreeding has scrambled their gene pools confusingly.*

If named cannabis varieties are not what they seem, standardized testing of cannabis samples presents an even more dismal picture. As expected, in the complete absence of federal regulation, labeling requirements vary tremendously among different US states, and even their enforcement is inconsistently applied within states. Consequently, testing of dispensary marijuana reveals disparities and confusion. For example, without even getting into the complexities of DNA analysis, the same named variety from different dispensaries often differs substantially when the underlying chemovar is identified by its cannabinoid/terpene signature.[7] A batch of Girl Scout Cookies buds from dispensary A may be a completely different chemovar than the same-named product sold in nearby dispensary B. Correspondingly, some strains with different names turn out to be almost identical from a chemovar perspective. This parallels what we saw earlier in the genetic realm with the Afghani/Jamaican, indica/sativa confusion. Some dispensaries quantify a restricted range of cannabinoids and terpenes, while others are more in-depth in their listings. But the choice of laboratories used for their assays is often up to the dispensary owner. Different laboratories use different assay procedures that in turn have different levels of reliability. So it's not unknown for dispensaries to have a new batch of buds tested by several labs and then conveniently pick the assay that yielded the highest THC percentage. How the contents are reported also occurs with widely varying levels of precision. One dispensary listed flower with a range of THC content of "13%–30%." Chemical testing of cannabis plants in reliable laboratories that use more scrupulous procedures reveals a number of unexpected findings. One is that, even within a single cannabis bud derived from one plant, there is a gradient of THC, with the highest concentrations at the tip.[8,9] Dr. Nirit Bernstein of the Volcani Center in Israel is an expert on cannabis cultivation. She says, "If we look at a tomato, some parts will be sweeter or will contain more lycopene, but it doesn't matter because it all goes in the salad or the ketchup. With medical cannabis, if one piece has twice as much THC it's too strong a dose and if another piece has less THC the dose will not be effective. So, our main goal is to learn how to grow plants to increase standardization for medical use." [10] Another problem is that there are surprisingly few studies on which particular agricultural growing practices produce optimal amounts of cannabinoids. One might assume that the healthiest, plumpest, best-nourished cannabis plants contain the highest concentration of desirable compounds, but that's not necessarily the case. Recall that in the wild the greatest amount of cannabis resin is produced by stressed plants at high altitudes. So perhaps plants produce better yields when exposed to a moderate amount of neglect. Dr. Bernstein's controlled research suggests that is the case.

Because CBD and THC are completely odorless, consumers perceive differences among cannabis varieties based primarily on aroma, and they make choices regarding potency, price, and likelihood of purchasing based on this information.[11] In turn, these important aromatic differences are almost completely dependent on terpenes.

Meet the terpenes

So, what are terpenes? Why are they important; what do they have to do with cannabis; and what, if any, are their major psychoactive effects and purported health benefits?

I've always been attuned to tastes and smells. Friends accuse me of having been a dog in a prior life. I'm the guy who spent an entire morning in my brother-in-law's Body Shop cosmetics franchise trying to mix the perfect blend of musk, sandalwood, and citrus. As a 6-year-old, I remember accompanying my parents to a perfume factory in Grasse in the South of France and spending an afternoon of vivid olfactory bliss among mountains of rose petals and dried lavender flowers. When the McCormick spice factory in downtown Baltimore moved to Baltimore County's Hunt Valley, I looked forward to the daily symphony of spice and flavor chemicals that the wind blew my way on my drive home. Subsequently, as part of a set of experiments I set up at Johns Hopkins Hospital to measure people's memory for odors, a handful of us from my laboratory journeyed to the McCormick plant. We sought their donation of a variety of pleasing- and nasty-smelling liquids that we could use in our odor-detection research. The day we arrived at McCormick, dozens of trained tasters were diligently sampling and rating, from identical tiny plates, hundreds of candidate recipe morsels for a new variety of bacon bits. For our own gustatory initiation, my laboratory members and I were each given an orange-colored, orange-tasting hard candy and asked to say what flavor we thought it was. We responded unanimously with "Orange, of course." The correct answer was "lemon." We had all been fooled by the citrusy flavor paired with the orange color cue. And incidentally, one of the chemicals that makes lemons smell "lemony" is the terpene compound limonene that appears prominently in the cannabis variety lemon haze.

Terpenes are strong-smelling carbon-containing (organic) compounds produced by many plants (including trees) and by some insects. They are major ingredients in so-called essential oils. The word "terpene" sounds like "terrapin" and "turpentine," but the name is derived from the latter substance and not the feisty little reptile. Turpentine is an oily evergreen-scented liquid made from distilled pine resin. It is one ingredient in Vicks VapoRub. Turpentine has also been used in medicine for millennia to kill worms in the gut and as "pine tar" for skin problems. If you've ever been unlucky enough to swallow any turpentine, you will know that it tastes disgusting and burns the tongue. If you swallow a really hefty dose, it can damage your kidneys and make your pee smell like spring violets. As Al Capone could tell you, turpentine was also an ingredient of bathtub gin during

Prohibition.

Terpenes pop up all over the natural world. Terpene trickery is used by a variety of insects to communicate and to deter insect predators. These chemicals can have marked effects on insect behavior.[12] Swallowtail butterflies, and some species of ants and termites exploit this characteristic. Some termites squirt terpenes directly onto potential predators, for example. During a hike in the foothills of the Swiss Alps, a Swiss friend had me gently poke an ants' nest. He encouraged me to sniff as the tiny, alarmed, scurrying insects released a terpene odor redolent of lemon zest, lemon verbena, and citronella. "Predators, get lost" was their message. The lemon smell from citronella ants is citronellol, whose odor according to textbooks resembles that of lemongrass and kaffir limes. Humans have copied citronellol's insect-repelling properties to make antimosquito citronella candles. Some species of butterflies have also gotten in on the act, terpene-wise. Merely sitting quietly on a leaf, tiger swallowtail caterpillars already look threatening to would-be predators. Some species bear black or yellow eyespots that make them resemble a tiny angry snake. Other related swallowtail caterpillars, looking strikingly distinguished in stripy coats of yellow, green, and black, conceal within their body folds twinned orange-yellow colored tonguelike structures. If you gently poke or harass such a caterpillar, it will unfurl both these almost-fluorescent organs that look like they were made from a melted cantaloupe jellybean. Once deployed, they emit a terpene odor redolent of orange peel and spice (from limonene and myrcene) accompanied by a funky smell of rancid butter. This combo is a highly effective predator deterrent. Other swallowtail cousins lack this specialized organ and repel predators by other mechanisms. Those with the structure possess an expanded gene cluster whose DNA codes for a series of terpene-synthesizing enzymes, similar to those found in cannabis trichomes.

Thousands of different plants manufacture terpenes, for similar predator-deterring purposes. Terpenes, in fact, are among the most widely distributed secondary compounds (ones not essential for key functions such as photosynthesis) in plants. They are responsible for the pleasant odors given off by pine trees and herbs, and they are the principal ingredients in perfumes and essential oils. When you walk into a pine forest, that characteristic fresh green smell is mostly terpenes, particularly alpha-pinene and D-limonene. Some have been used by humans for hundreds of years as ingredients in scents, cosmetics, and flavors. These fragrant oils are not synthesized by botanicals for our olfactory enjoyment but are important plant defenses. At high concentrations, some terpenes can be toxic to predators and disease-causing organisms. Thus, in nature, they protect plants from bacteria, fungi, insects, and a variety of other environmental stressors, including would-be herbivores. Individual terpenoid compounds with high insect-repellent activity include alpha-pinene, limonene, citronellol, citronellal, camphor, and thymol. In cannabis plants, terpenes—perhaps two hundred of them[6]—are secreted for the same defensive purposes from the resin glands that also produce cannabinoids.

As you walk into a citrus grove, pine forest, or cannabis growery, the perceptible chemical haze and many of the characteristic odors are produced by terpenes. In plants, these aromatic essential oils are squirreled away in specially designed segregated containment structures (such things as oil tubes and glands, including trichomes). These storage areas may also protect the plant from its own toxins. Plants manufacture terpenes as the Swiss Army knives of botanical defense. They repel and even kill insects, discourage grazing and browsing by animals, and are plant antibiotics in terms of reducing infection. Pinene, for example, is an antifungal. Other terpenes used in some plants attract pollinators such as insects and bats, but wind-pollinated cannabis obviously has no need of these chemical attractions. CBD and THC have no odor of their own, so cannabis terpenes explain why skunk varieties smell "skunky" and super lemon haze smells "lemony." The characteristic olfactory signature of different cannabis strains is due entirely to the terpene compounds that the plants brew in their trichomes. The aromatic qualities they instill within marijuana flowers provide the bouquet that budtenders, given an ounce of encouragement, are apt to describe in flowery language. The cannabis plant is not just a one-trick pony that exists to produce THC and CBD. It is a complex, busy chemical factory producing hundreds of compounds. The more we probe, the more we realize that many of these chemicals affect the quality of the cannabis "high," the plant's widely varied medicinal applications, and the profile of the accompanying side effects, both desirable and undesirable.

I had always thought of the terpenes in cannabis as amusing little ornamental chemicals along for the ride, in terms of providing the chemical basis of taste and smell, but contributing nothing substantive to the essential qualities of the "high." Their presence, I believed, was merely to intrigue geeky factoid-hoarders and cannasseurs. As an analogy, I would have rated the knowledge similar to being aware that David Bowie had one blue and one brown-appearing eye—an interesting tidbit, totally irrelevant to his musical performance. But I was wrong. About the terpenes, that is. Terpenes have their own distinct story to tell beyond exhibiting mild psychoactive effects comparable to aromatherapy. Incidentally, many of them are ingredients in aromatherapy oils, perfumes, and essential oils. Their independent, individual psychoactive effects and their interactions in boosting, lowering, or modulating THC-related behaviors are not yet well studied and deserve further research. If we think about it, a simple push-and-pull relationship between THC and CBD seems insufficient to explain the wide variety of things cannabis does to our body and mind. To give even a simple example: why do some chemovars seem to unleash the energy of Lucifer while others usher in the torpor of Rip Van Winkle? Outside of the large number of cannabinoids, only partly explored in terms of their effects on human physiology and most of which are not tracked in standard assays, terpenes likely offer an important part of the explanation. It is likely that there are synergistic effects between terpenes and cannabinoids, known as "entourage effects," a term frequently bandied about by budtenders. The underlying concept is that the entire terpene-plus-cannabinoid

mélange contributes interactively and is responsible for the resulting high.[13–16] As we will learn, terpenes may both modify THC and CBD metabolism in our bodies and have their own independent psychoactive properties. Terpenes can affect mood, arousal, and pain sensitivity. Some terpenes such as beta-caryophyllene even bind directly to cannabinoid receptors in our nervous systems. So to understand the whats and whys of the terpene universe, let's take an informative detour into the chemical world.

Where and how are cannabinoids and terpenes synthesized in the cannabis plant?

Chemical synthesis, meet botany. For those of you like Sam Cooke, who don't know much biology (and would prefer not to), the bottom line of the following paragraph is that both cannabinoids and terpenes are manufactured inside the cannabis plant as different products via substantially overlapping chemical pathways.[3] Or as one source phrases it, they "share a common biosynthetic origin." [6] The operating instructions in the plant's genes can make relatively simple molecules (terpenes) or more complex ones (cannabinoids) from the same stockpile of ingredients. Furthermore, many of the essential terpenes involved in this process are delicious-smelling oils and resins named for various non-cannabis plants ranging from lemon to guava, where they are also produced. In cannabis, all this chemical transmutation takes place in the lollipop-shaped trichomes of the female flowers.

If you're more interested in the twists and turns of the molecular operations by which the plant makes the ingredients over which budtenders and cannasseurs wax poetic, we begin with a compound called "farnesol." Farnesol is named for a flower extract from the Farnese acacia tree that is used in perfumes and deodorants. The Italian Renaissance Farnese family (which included Pope Paul III and numerous dukes of Parma) constructed beautiful botanical gardens in Rome. Within their walls, this particular Caribbean tree was cultivated by Cardinal Odoardo Farnese and thus named. It is also synthesized in the human body and reacts on many receptors in cell nuclei.[17] Farnesol's chemical relative in the cannabis plant, farnesyl diphosphate, is converted by enzymes into sesquiterpene compounds. These include beta-caryophyllene (a food flavoring found in black pepper that is incidentally the compound that drug-sniffing dogs zoom in on) and alpha-humulene (named for hops). The chemical building bricks used to assemble farnesyl diphosphate can alternatively be used to build geranyl diphosphate (named for the showy red or white pelargonium geraniums whose blooms are rich in the chemical and decorate Swiss window boxes). In turn, geranyl diphosphate is the chemical building block used to synthesize a whole series of monoterpenes, many named for the plants that produce them in large quantities. These include beta-myrcene (my speech software helpfully rendered that as "murder scene"), named for the myrcia plant. Along with cloves, guava, allspice, and eucalyptus, myrcia is a member of the myrtle family. Other examples here are alpha-pinene

(named for pine trees) and limonene (named for lemons). Not content with its role in monoterpene synthesis, geranyl diphosphate is also used by the cannabis plant to assemble cannabigerolic acid, usually abbreviated to CBG. (Incidentally, CBG should not be confused with the legendary New York punk music venue CBGB.) Depending on which synthetic enzyme carves it up, CBG is transmuted either into tetrahydrocannabinolic acid (THCA) or cannabidiolic acid (CBDA). With a little bit of heat and the addition of carbon dioxide, these magically become THC and CBD, respectively.

All this chemical synthesis occurs in cannabis trichomes. There are various trichome types on the plant, but the important ones are glands on the end of a long stalk, with the whole apparatus resembling a mushroom or lollipop. When I say "long stalk," this is speaking relatively; an entire trichome is barely visible with the naked eye. Thousands of these tiny sparkly resin factories are packed on the surface of the flower bud, where they participate in an active dialogue between the plant and the environment.

Trichomes (the term derives from the Greek word for "hair") are hardly unique to cannabis: they exist on about one-third of all plants. Under the microscope, trichomes from different plants can resemble thorns, needles, hooks, or mushrooms. When you grab a stinging nettle, the needlelike hollow stinging hairs injecting you with itch-inducing painful nastiness are pointy trichomes. Other plants store important secretions they have manufactured in tiny bulbs or glands on the end of hairlike structures. These mushroom-shaped structures are called "glandular trichomes," for obvious reasons. Plants use them as mini-factories to manufacture chemicals they would like to keep on their surface, often to deter pests of various kinds. Some of them protect plants from other potentially harmful things in the environment, such as ultraviolet rays or excessive heat. Plants have an inherent drive to make these chemicals, and if attacked by insects or burned by the sun, they will bump up production accordingly.

From our cannabis-centered perspective, glandular trichomes are especially important because many of the specialized compounds produced in this way are terpenes. Many plants, including mint, tomato, tobacco, petunia, hops, and cannabis, all manufacture terpenes in these specialized structures. In the case of cannabis, the glandular trichomes synthesize both terpenes and cannabinoids in the form of resin. Trichomes use both their chemical and physical powers to guard the plant from insects and browsing animals, and from drying out. This is what you might call their "resin d'être." THC and CBD, being tasteless and odorless, do not deter disease-causing organisms. Terpenes perform this function effectively. Fungi and bacteria are killed by limonene, insect pests repelled by geraniol and killed by caryophyllene, while herbivores such as sheep find pinene distasteful. For the cannabis plant, the nonchemical physical part of its defense exists in a separate set of non-glandular trichomes. These guys resemble tiny needles or teardrop-shaped mini-thorns. If you rub your finger across the cannabis leaf, it feels distinctly rough, a little bit like sharkskin. This sandpapery texture is the non-glandular trichomes making you aware of their presence. These gritty structures effectively

deter munching insects, crawling caterpillars, and egg-laying plant parasites. (Other plants take this a whole step further. The needlelike trichomes found on nettles offer additional protection, even against large mammals.)[18] Cannabis plants are thus equipped by evolution with multiple predator-deterring mechanisms. A hapless insect zooming in to munch a leafy hemp snack or to lay its eggs may unwittingly be trapped in sticky resin, have its body pierced or its legs ripped off by spiky trichomes, or be poisoned by terpenes. Plants are tougher than we think.

As cannabis flower buds mature, the chemical processes described earlier proceed busily, and the glands gradually change their appearance from milky white to clear and then finally to a beautiful shade of liquid amber. That color matches the changing stigmas as they ripen from white to orange yellow. As Alexandre Huchelmann and his group stated in 2017, “Understanding the way glandular trichomes develop to finally turn into highly efficient biochemical factories in the epidermis of non-model plant species is of key importance and could lead to more applied outcomes.” [19]

One truly tantalizing ontological question is why the cannabis plant bothers to make cannabinoids. We don’t know the answer to that question, so just this once, let’s speculate with a plausible just-so story. Like many plants in the botaniverse, cannabis started off making terpenes for the usual predator-deterring purposes. Due to some random evolutionary coin toss, the plant changed an existing gene’s DNA slightly. This alteration allowed some cannabis plants to make a new enzyme that synthesized cannabinoid precursors from the same chemical toolkit it had always used to manufacture terpenes. The small extra step conferred evolutionary benefits. The modified cannabis plants were better protected from UV light and from heat, and perhaps able to trap or disable insects more effectively. In turn, this allowed plants with the altered genes to expand their territory higher up the mountainside and into hotter, dryer areas. The modified plants were then chosen by natural selection for these beneficial features and thrived. After a few millennia, when early humans came along to exploit hemp plants for fiber and seeds, they discovered medicinal and psychoactive properties in the cannabinoid-manufacturing cannabis plants as an added benefit. These latter properties were yet another reason people cultivated the plant and spread its seeds wherever they migrated. An imperfect analogy might be a blacksmith who makes nails for horses’ hooves in his forge. One day, after a random accidental hammer misstrike, he realizes if he copies that one extra step and bends his nails into a circle, then he can sell them for 10 times the price to tourists as decorative handcrafted rustic finger rings.

Because we use them in other contexts as flavors, perfumes, and essential oils, the terpenes found in cannabis are legal to purchase. Many are approved by the FDA as additives to food or cosmetics. Anyone can go online and buy them individually by the bottle or in blends that mimic the odor profile (and by extension the chemical and perhaps behavioral fingerprint) of well-known cannabis chemovars. For a little over $20 you can purchase the blended liquid terpene profile of Super Lemon Haze, Dogwalker OG, or Blue Dream. These little

bottles of fragrant bliss contain blends of pure food-grade botanical terpenes that more or less mimic those found in particular chemovars. For example, Lemon Skunk's terp profile blend from Trim Buddies is 97% limonene with small amounts of beta-caryophyllene and myrcene, plus a tiny sprinkle of other terpenes. So a reasonable question is whether assembling a recipe mimicking the proportions of cannabinoids and terpenes found in a given chemovar will replicate its behavioral profile. Or, put another way, will a couple of squirts of lemon skunk essence out of a bottle spritzed on to a bowl of average street weed replicate precisely the buzz obtained from high-end Lemon Skunk? The answer to that question turns out to be complicated.

The average person thinks of individual chemical compounds as having straightforward, perhaps unique effects. Logically then, dosing with a mixture of compounds will produce the sum of their effects but nothing more. Example: Valium makes you relaxed, and ecstasy (MDMA) lovey-dovey. Therefore, Valium plus ecstasy should make you super-chilled and extra cuddly. If only life were so simple. In reality, different compounds taken together frequently either boost or undermine each other's effects. A well-known example comes from the medications given to combat HIV, where drug "cocktails" of several virus-killing medications proved to act synergistically in ways that were effective significantly above and beyond those of each drug alone. Analogously, psychological effects resulting from cannabis are often said to rely on entourage effects. In addition to the complicated rivalry between THC and CBD, terpene compounds also have biological effects that interact with those of phytocannabinoids in ways that are only just beginning to be studied scientifically. Budtenders use PhytoFacts to describe terpene content and behavioral effects.[4] But let's dive a little deeper into the terpene pool.

Terpene chemistry

There are around 200 total terpenes in the cannabis plant.[16,20–23] Approximately 50 of them are commonly found in cannabis sold in the US, out of which 10 or so are commonly quantified for dispensaries. Even the best assay laboratories max out at around 20 terpene assays, or only 10% of the theoretical total. In discussing cannabis terpenes, I will explore a small handful in detail because of their special interest or unusual properties. In regular flower cannabis, terpenes account for 2%–5% of total weight. Many chemical extraction methods (like those we encountered in the Denver growery) produce relatively pure samples of THC or CBD for use in dabs. Terpenes boil off at different temperatures and are harvested separately, usually early in the purification process. Typically, the final THC concentrate extracts will have terpenes blended back in, separately adding aroma and flavor. Terpenes typically constitute around 10% of the final wax or shatter product. Because terpenes are oil- and alcohol-based, the more of them added back to a concentrate, the more waxy and pliable and the less brittle is the resulting product.

Terpenes are classified by chemists in terms of their molecular structure. The basic chemical skeleton on which all terpenes are built is the 5-carbon compound isoprene. If you polymerize this stuff, you end up with old-fashioned rubber, as in car tires. Among the simplest members of the terpene family are monoterpenes (confusingly named since they consist of two isoprene units, not one), which contain 10 carbon atoms. Monoterpenes include pinene, myrcene, limonene, linalool, and geraniol. Sesquiterpenes are constructed out of three isoprene units. These 15-carbon compounds include caryophyllene, nerolidol, humulene, and guaiol. All these terpenes are found in cannabis flower buds.

Along with having their own molecular characteristics, terpenes are the building blocks of other increasingly complicated chemical groups. For example, *terpenoids* are related, slightly more complicated chemical structures containing additional chemical groups. And, molecules doubling the complexity of sesquiterpenes (termed "triterpenoids"), such as squalene and friedelin, have at their core six isoprene units. Confusingly, many people (including many chemists) refer to all terpenes and their kin under the general term "terpenoid." Even more confusingly, others use the term "terpene" as a catchall to include both terpenes and terpenoids. Let's tiptoe past this troublesome terpenoid terminology to clarify that the triterpenoid compound friedelin, found in the roots of cannabis plants, is the only known member of this family found in marijuana. But the reason I mention the terpenoids—and it's an important one—is that after further judicious molecular tweaking and even more chemical complexity, the whole family of cannabinoids is synthesized from them within the cannabis plant.

Terpenoids, like terpenes, are compounds we encounter every day. They contribute to the scent of eucalyptus; the flavors of cinnamon, cloves, and ginger; the yellow hue of sunflowers; and the red color of tomatoes. Well-known terpenoid molecules include citral, menthol, camphor, chemicals found in the ginkgo biloba tree, the curcuminoids found in turmeric and mustard seed, and the hallucinogenic chemical salvinorin A derived from the plant *Salvia divinorum*. Incidentally, inside our bodies, even more complicated and usually considerably less odorous chemicals than found in the living world are built from them. The triterpenoid molecule squalene, for example, is the main precursor that we use to biosynthesize steroids such as testosterone, as well as vitamin A (a tetraterpenoid), which is a few more steps down the synthetic chain.

Genes found in dozens of plants and insects are able to synthesize terpenes. They achieve this by using enzymes logically enough known as "terpene synthases." The same enzymes found in our livers that help break down harmful products in our food and metabolize many of the pharmaceuticals we ingest, including terpenes, also modify the synthesis of terpenes in plants.

Back to cannabis. It has been recognized in the last few years that, for we humans, terpenes are not just inert compounds but can sometimes bind to or modify CB_1 or CB_2 receptors. For example, the terpene beta-caryophyllene binds quite tightly to CB_2. Terpenes may also modify the permeability of the blood-vessel barrier that acts as a living filter between the brain and the rest of the

circulation for cannabinoids such as THC and CBD. This alteration results in letting more or less of these cannabinoids cross into our brains. Finally, terpenes may even alter the metabolism of cannabinoid compounds. All these facts raise the probability of cannabis entourage effects being a genuine phenomenon.

What are behavioral effects of terpenes in humans?

Until recently, we knew very little about this question, but terpenes may possess independent psychoactive effects in the absence of cannabinoids. And as we just saw, they can interact with psychoactive cannabinoids regarding their metabolism, receptor binding, and passage across the blood-brain barrier. It's an open question whether terpene effects on behavior are best studied in the lab in specimens taken from cannabis plants or by adding precisely measured amounts of purified terpene compounds prepared by a chemical manufacturing company. Nobody has actually tested this. The fate of terpenes in the body is complicated. As they are metabolized by the liver, they are broken down into new compounds, some of which have novel biological activity.[20]

Chemical activity at cannabinoid receptors is one way that terpenes can influence our behavior. Another means by which they affect our moods and bodily states may be as odorants, like essential oils. Eva Heuberger has shown how odors affect the brain's electrical activity, as assessed by EEG.[20] For example, certain odors alter the slow theta rhythm generated primarily by our memorable friend the hippocampus. Theta activity increases when animals sniff things in their environment, and the hippocampus encodes smell data along with memory and emotional, motor, and cognitive activity associated with the odor. Dogs map the world this way. Humans are much less sensitive to odors than many other mammals, but EEGs show we also respond differentially to different-smelling compounds, including terpenes. Although both budtenders and aroma therapists claim that some terpenes and essential oils are "relaxing" and others "energizing," the results of many studies on this topic are very hard to interpret, and results frequently contradict each other. So terpenes in cannabis may affect our moods and behaviors through our sense of smell, but no one has shown that convincingly.

A summary of what's known regarding terpenes and their interactions with other cannabinoids is outlined in Russo's paper.[24] He explores their synergy with THC, effects that can include both facilitation and antagonism. Low concentrations of terpenes can be potent behaviorally; this would seem to be necessary since concentrations in the plant are often relatively low. Terpene effects are strongest when the compounds are inhaled, and they may be absent when the compounds are taken orally. Interestingly, cannabis samples provided to researchers by the National Institute on Drug Abuse are relatively devoid of terpenes, containing approximately eight times fewer than equivalent dispensary-purchased flower.[24]

Having discussed some of the ways that terpenes in general may affect us, let us review some of the commoner terpenes and their effects one by one. A word of

warning though: many of the claims made regarding terpenes have little experimental backing despite being frequently touted. Where there is good evidence to support health-related effects, I have tried to provide the relevant citations, but that is the case for a minority of the compounds described. Currently, many of the claims about cannabis terpenes are at a level of folk wisdom rather than science.

Monoterpenes

Alpha-pinene smells sharply "green" like the odor of pine trees and turpentine. It is among the commonest terpenes found in cannabis. Physicians have long believed that pinene can reduce inflammation and open up airways in the lungs (hence the use of turpentine and Vicks VapoRub for people with chest complaints). This compound is found in conifer trees, including in pine needles, as well as in the herbs rosemary and parsley. Alpha-pinene is prominent in the cannabis chemovars Jack Herer, Strawberry Cough, Romulan, Blue Dream, and OG Kush. Unexpectedly, it is an acetylcholinesterase inhibitor (it inhibits the metabolic breakdown of acetylcholine, a key brain neurotransmitter).[25,26] Among other functions, acetylcholine helps underpin memory. Pinene's inhibitory property is shared with medicinal compounds with similar but much stronger activity prescribed by physicians to help slow memory loss in patients with early Alzheimer's disease. Theoretically, pinene may help with memory decline or boost memory and alertness.[27,28] Pinene is also purported in terpene charts displayed in dispensaries to promote alertness and to be a cognitive stimulant. The actual evidence for all these claimed effects is thin, and the topic needs to be much better studied and quantified objectively. To complicate things, cannabis also contains compounds (including THC) that block acetylcholine receptors and inhibit acetylcholinesterase, which would therefore logically impair short-term memory.[3] Indeed, such amnestic effects were demonstrated in a careful placebo-controlled study of pure THC.[29] To further muddy the waters, pinene's inhibition of acetylcholinesterase is multiplied by the effect of other terpene-like compounds, including camphor.[25] Which cannabis chemical wins this brainy tug-of-war over acetylcholine may well vary from one chemovar to another.

Alpha-pinene has an interesting backstory. It is found abundantly in the common juniper shrub, whose somewhat bitter, resinous, fragrant-smelling berries add most of the flavor to gin; it's also found in larger, upright, tough-as-nails juniper trees, whose leaves, twigs, and cones constitute the main diet of the wild rodent known as Stephen's woodrat. These footlong rats dwell in the US in the juniper woodlands of Arizona, New Mexico, and Utah, and across the globe in other dry juniper-heavy woodlands. Stephen's woodrats are rather endearing creatures, with large dark, soulful eyes, delicate feet, big rounded ears, and long feathery tails that resemble grayish, furry stalks of barley. Like archetypal stoners, they are more active at night, are sleepy during the day, move relatively slowly, and are known for their noisy chatter. They are attracted to bright shiny objects

such as sparkly rocks and soda-can tabs that, given their destiny as pack rats, they cache in their complicated twig nests. They are also notoriously distractible. Anyone who has witnessed one discard a juicy-looking juniper cone in favor of a sparkly button, only to trade that a minute or two later for a tempting berry, will be struck by this behavior. Unlike caricature stoners though, they are literally "bright eyed and bushy tailed." This woodrat, one of a dozen species found in the United States, is of particular interest to us because its diet consists of 90% juniper, from the crunchy foliage to the fleshy, waxy cones. Thus, at any given time, one might expect the Stephen's woodrat's body to be awash in terpenes, especially pinene. Since terpenes are synthesized by trees and plants to deter animal and insect predators, it is logical to ask why these creatures would choose an exclusive terpene-enriched diet. The answer is that, compared to other species of woodrats that eat more promiscuously, evolution has equipped Stephen's woodrat with plentiful liver enzymes and probably specialized gut bacteria targeted specifically at breaking down terpenes and other toxins located in junipers. So the rats can benefit from the tree nutrients undeterred by terpenes.

Back to gin: like cannabis, gin at various times in its long history has been a medicine, recreational compound, fad consumption item, and social hot-button issue. Those who disdain gin's flavor might accuse the beverage of tasting like a cheap Christmas-tree air freshener. That's not far off the mark; the same terpenes that live in Christmas trees (and of course juniper berries) permeate this alcoholic spirit. In traditional pot-distilled gin, the still workers batch-distill neutral spirit and put in carefully measured amounts of botanical ingredients—predominantly juniper berries—to soak and impart their flavors and fragrances, before redistilling the mash. In case you were wondering, it's called a "pot still" not because of any distant connection to cannabis but because of the traditional alchemists' alembic-shaped copper pot in which the ingredients are heated. There is a weed connection, however. Gin contains multiple terpenes derived from juniper berries; as an informed woodrat could tell you, these are many of the same terpenes found in cannabis and include alpha-pinene, limonene, beta-myrcene, and alpha-terpineol. The first two terpenes impart a piney, woody, citrusy bouquet, while the third adds a more in-your-face herby, skunky, twiggy, slightly resinous flavor. Many gin distillers add coriander as an additional flavoring. This contains terpenes linalool and geranyl acetate, also found in cannabis. These compounds add flowery, lavender-like, spicy, and rose-scented notes. A few brands add dried citrus peel to dial up the limonene, or other botanicals containing yet other terpenes. German gin-distilling purists disdain flavor ingredients other than juniper berries; in fact, German law forbids further additions.

Because of human environmental exposure to pinene from cypress, cedar, and pine trees used in building, furniture, and decorative materials, there is a fair amount of laboratory research on effects of pinene exposure on humans. This work has been done primarily to assess its safety, but several of these studies offer additional clues to behavioral effects. Sawmill workers in Sweden are famously exposed to large amounts of pine-derived terpenes by breathing in the coniferous

fumes as they saw and stack raw lumber. They have thus been the subject of many pinene-related health studies. A 1990 article measured the uptake, distribution in the body, and elimination of alpha-pinene at various concentrations in human volunteers.[30] These laboratory subjects sat in an exposure chamber two at a time and breathed in different amounts of pinene for two hours while they gamely pedaled away on an exercise bicycle. Because the compound is fairly soluble in blood and fat, around 60% of the terpene was absorbed into the volunteers' bodies, at proportionately greater amounts as concentrations rose. While a proportion of the chemical was rapidly metabolized, some was sucked up into fat and stayed there. The investigators estimated that it would take more than two days for the body to completely eliminate it. The Scandinavian scientists focused mainly on lung-related effects of the inhalation (which turned out to be trivial). Unfortunately, they pretty much ignored behavioral effects, so we have no idea whether the subjects inhaling high doses felt stoned or especially alert (bright eyed and bushy tailed, in fact), had better memories, or perhaps were more attracted to bright shiny objects.

Work by others has shown that pinene reduces activity in the prefrontal cortex and induces feelings of comfort. In 2016, Japanese investigators exposed 13 young women to alpha-pinene vapor and showed significant effects on heart rate (which fell significantly) and heart-rate variability. Both these changes were consistent with physiological relaxation mediated through the parasympathetic nervous system.[31] So although pinene is billed in dispensaries as increasing alertness, what little evidence we have suggests more that it may be a relaxant.

Beta-myrcene: This monoterpenoid is the most prevalent terpene in many cannabis chemovars in the United States and Europe.[3] It is also present in hops, lemongrass, citrus fruits, mango, and thyme. It smells skunky and musky, with slight lemony, fruity undertones. Beta-myrcene is in fact what makes skunk cannabis smell "skunky," although actual four-legged stripy skunks defensively squirt a completely different stinky chemical. Beta-myrcene is said to have moderate sedative and (somewhat weaker) pain-relieving and anti-inflammatory properties. If any terpene is responsible for couch lock, this soporific, muscle-relaxing, and mildly hypnotic compound is the likely culprit.[24] There is some evidence that it may enhance psychoactive effects of THC. This musky terpene chemical can be found relatively prominently in indica chemovars. Skunk XL, White Widow, Green Crack, and Blue Dream are said to contain relatively high percentages.

Now we'll examine briefly some miscellaneous terpenes worth mentioning because they are frequently listed in dispensaries. *Terpinolene* is found in parsnips, citruses, mint, sage, rosemary, juniper, cumin, lilac, apples, tea tree, nutmeg, and conifers. This minty-tasting terpene emits an aroma described as woody and smoky, with a hint of lilac and apple blossom. It is found in the chemovars Girl Scout Cookies, OG Kush, and Jack Herer. Traditionally—that is, as conveyed by budtenders—terpinolene is said to be sedative and partly responsible for couch lock, consistent with experiments in mice.[32] Other reports,

however, suggest confusingly that terpinolene-dominant chemovars were consistently rated as energizing.[3] Such disparities in terpene effects are another reminder that properly controlled double-blind studies of single and multiple terpenes need to be carried out.

D-limonene is found in citrus fruits (especially their rinds), juniper trees and shrubs, and peppermint. Unsurprisingly, it smells like lemon oil. As mentioned earlier, it is manufactured along with related compounds by some insects such as ants. Limonene is purported to be a stimulant. There are suggestions that it has effects on adenosine receptors in the brain that are connected to wakefulness. These receptors are where the caffeine in coffee acts to keep us awake. One report claims that this terpene helps turn unhealthy white body fat into more healthy brown fat. A major terpene in citrus fruits as well as in cannabis, limonene has been used clinically to dissolve gallstones, to improve mood, to relieve heartburn and gastrointestinal reflux, and as an anticonvulsant; it has also been shown to destroy breast-cancer cells in laboratory experiments. In addition, its antimicrobial action can kill pathogenic bacteria and perhaps fungi.[33] It is prominent in Super Lemon Haze, Sour Diesel, and OG Kush.

Ocimene is a pleasant-smelling terpene used in perfume. Little is known concerning its behavioral properties. *D-linalool* is a terpene found abundantly in the lavender plant. Its pleasant characteristic floral smell contributes a fair amount to marijuana's characteristic odor. It is purported to have anticonvulsant, mildly sedative, calming, and relaxing properties, and it may aid in skin absorption of THC and CBD. It is a reputed anticonvulsant, and it also amplifies serotonin-receptor transmission, conferring a possible antidepressant effect.[34] It is prominent in the chemovars Lavender, Amnesia Haze, Special Kush, and Skywalker. *Geraniol* is found in many flowers, fruits, and vegetables, including oil of geranium, tobacco, and rose oil. This terpene is pleasantly and sweetly floral with a faint citrusy, peach, and rose backdrop. These properties account for geraniol's use in perfume making. It is also used by flavor chemists to add fruity notes to foods and is commonly used in shampoos, soaps, and skin lotions. The compound repels mosquitoes and is said to be an antioxidant and neuro-protectant. Geraniol is produced by bees, who use it (among other compounds) to mark their territories. It may or may not have buzz-inducing properties. It is found in the chemovars Amnesia Haze, Great White Shark, Islands Sweet Skunk, and Master Kush.

Sesquiterpenes are 15-carbon compounds consisting of three isoprene units. Minor members of this group include *trans-nerolidol*, a secondary fruity- or floral-smelling terpene occurring in jasmine, tea-tree oil, and lemongrass. Its scent resembles roses and fresh apples. It is said to be sedative, antiparasitic, and antifungal. Trans-nerolidol is found in the chemovars Skywalker OG and Sweet Skunk.

A major sesquiterpene player is *beta-caryophyllene*. This spicy-smelling, somewhat volatile sesquiterpene compound is generally described as wood scented or like black pepper. It is found in several thousand plants, including black pepper (unsurprisingly) and cloves, hops, oregano, rosemary, basil, cinnamon, and

many green leafy vegetables and fruits.[35] Beta-caryophyllene, or BCP for short, is also synthesized by the artemisia (wormwood) plant, which is used to flavor absinthe and is used in clove and cinnamon chewing gum. The pure compound is a pale yellow oily liquid that barely dissolves in water and vaporizes at a relatively low 266°F. BCP is one odor that sniffer dogs key in on when searching for illicit substances. Perhaps coincidentally, one of the prominent chemovars expressing notable BCP levels is in fact Chemdawg, along with Girl Scout Cookies, White Widow, OG Kush, Super Silver Haze, Skywalker, Bubba Kush, and Sour Diesel. Almost uniquely among terpenes, BCP indisputably interacts with the peripheral CB_2 cannabinoid receptor system. BCP may be mildly sedative, and there are claims that it is an antioxidant, anti-inflammatory, and pain reliever, and that it kills parasites and their larvae. There is preliminary evidence that BCP has antianxiety properties and that it reduces alcohol cravings in mice. It is also claimed to be gastro-protective and good for treating certain ulcers; it also shows promise as a therapeutic compound for inflammatory conditions and autoimmune disorders, perhaps because of CB_2 interactions. At least in rats and mice, BCP is notably effective at reducing both acute and chronic pain. It may have a future role as a safe painkilling compound in humans.[36]

Humulene is a terpene found in hops, coriander, basil, and cloves; it vaporizes at a very low 222°F. Humulene smells "hoppy," earthy, and woody. People sleep on hop-stuffed pillows as a sleep aid; humulene may be sedative and soporific. It is also claimed to have anti-inflammatory and appetite-suppressant properties, and it may have inhibitory effect on cancer cell growth. The compound inhibits fruit-fly maturation, suggesting it is produced by the plant to deter potential insect pests.[37] Humulene is relatively overrepresented in strains such as White Widow, Headband, Sour Diesel, and Girl Scout Cookies. Finally, *guaiol*, with its low boiling point of 92°C, smells piney and occurs in cypress pine trees.

In summary, the world of cannabis terpenes is considerably more complicated than we once suspected. Terpenes are common across the plant kingdom, serving multiple adaptive and especially protective purposes. In the cannabis plant, these chemicals are believed to be primarily defensive against pests and diseases of various sorts. From the point of view of cannabis consumers, terpenes not only interact with cannabinoids in ways that have yet to be properly elucidated but likely also have their very own complex effects on thinking and behavior as well as on the drug "high." At least one terpene (BCP) interacts significantly with CB_2 receptors. Others have effects on the blood-brain barrier. Several terpenes possess promising medical potential. This is an area that remains wide open for scientific exploration, and it's probable that many reports on this topic will be published over the next few years.

Cannabis concentrates

For every single naturally occurring drug, ranging from opium to cocaine to THC, users seek more efficient methods to extract and concentrate the active chemical

principles on the route to a higher high. In the case of cannabis, concentrates are enriched preparations containing more of the desirable compounds than the parent plant contains. Depending on the extraction method, along with various cannabinoids, concentrates may also include proportions of terpenes and flavonoids. Because cannabinoids are fairly fat soluble, there is a fairly discrete set of approaches commonly used to harvest them from plant material.

The traditional method of enriching THC in countries including Morocco and Afghanistan is to manufacture hashish, commonly known as “hash” or “cannabis resin.” Hashish is composed of trichomes that can be collected and concentrated in a variety of ways. The time-honored approach is to press or rub female cannabis leaves or buds between one’s palms and roll the resins that stick to the skin into a small ball. The plant material can also be rubbed or sieved through screens or measures of varying diameter to yield a powder that can be molded into bricks using heat. Another method to strip off the trichomes is to use ice water; the little glandular hairs become brittle at low temperatures and can be sheared off by agitating the cold mixture. Because of their density, they sink to the bottom of the slush, from where they can be harvested. Depending on the chemovar of origin, hashish can contain anywhere from 5% to 25% THC. The consistency and color vary widely from paste-like to bouillon cube, and from yellowish brown through burnt umber to almost black. Easily the most interesting book I’ve read on the topic of hashish is Robert Connell Clarke’s comprehensive nearly four-hundred-page *Hashish!* [38]

The hash that I used in my birthday-cake recipe was the form by which most cannabis reached England in the 1960s and ’70s. Before the invention of efficient lighting and heating systems, it was a major challenge to grow cannabis plants in the unpredictable and frequently cloudy English weather. Importing floral marijuana was not efficient because of the relatively low THC content of a few measly percent back then and because of its relative bulk compared to the more concentrated, easier-to-conceal hash or khif. I remember an acquaintance showing up at a student party with a chunk of hash half the size of an average paperback book and as thick as an average McDonald’s hamburger. One surface was still covered with a layer of what appeared to be light gray paint. The most immediate origin of this illicit object had been the cabin wall of a Pakistani freighter that had recently docked at Newcastle. An entire wall panel had been carefully substituted with an equivalent amount of hashish that had then been carefully painted over to conceal its true nature. The French Connection had nothing to rival this.

More modern methods of concentrate production borrow from the same processes used to create essential oils (many of which are terpenes) and to decaffeinate coffee. Precise methods are always being tweaked in order to maximize the desirable chemicals in the concentrate and to minimize undesirable malodorous and nonpsychoactive ones such as chlorophyll.[39] The starting plant material needs to be carefully prepared in terms of how it’s harvested, dried, ground up, and milled—akin to grinding coffee for an espresso shot. The more plant material that can be packed into the extraction vessel, the more efficient and

cost-saving is the procedure, so high-end grinders and pulverizers are much sought after to yield precise particle sizes that stop the system from clogging up. One advantage of the extraction procedure is that the starting materials do not have to contain high concentrations of THC, so leaves can be used, for example. Outside of DIY procedures for making your own mini-quantities of rosin dabs at home using a hair straightener set to around 300°F,[40] the crudest scaled-up process involves using open-source illegal extraction techniques, sometimes referred to as "open blasting." Only slightly more refined is using butane solvent to create butane hash oil (BHO). Compressed butane liquid is what's found inside cigarette lighters. Because it's under high pressure and extremely flammable, there's always a danger of fires and explosions, so smoking cannabis during the preparation procedure is unwise. The essential steps in making BHO are heating the ground plant material with liquid butane solvent under increasing pressure and then sucking away the liquid from the marinade by evaporating it in a vacuum. The lowered pressure changes the solvent from a liquid to a vapor that is whisked away and recycled, leaving behind the concentrate. The process is only moderately effective. It is also marred by the fact that residual butane usually contaminates the concentrate; the chemical is unhealthy. BHO is preferred by some producers because the extraction process is relatively cheap and low tech. Liquid propane is sometimes used in a similar process to produce propane hash oil. Other related methods include using ethanol or isopropanol to obtain cannabinoids without using increased pressure, but these require finicky and exact manipulation of temperature and involve a rather lengthy procedure.[41] In addition, these methods are prone to suck out unwanted material from the plant, including chlorophyll and the type of bitter chemicals also found in fall leaves. Some chemists use activated charcoal to remove this nasty goop.

Supercritical carbon-dioxide processing is the extraction method used inside the Denver growery that I visited. This process is used to remove caffeine from coffee beans to produce decaf and in some dry-cleaning methods. Conceptually it is similar to the liquid-extraction procedures mentioned earlier, and it works by compressing the CO_2 gas to the point where it has qualities of both a gas and a liquid, and it acts as an effective solvent. At this stage, the carbon dioxide is pushed through an extraction vessel loaded with ground-up cannabis-plant bits. The procedure is more chemically gentle and safer than those I've described so far. It's also more "tweakable" in that by subtly varying the temperature, pressure, or extraction time, one can more selectively remove particular cannabis compounds. Once these are obtained through repeated extraction cycles, then the CO_2 can be routed back into a condenser, converted back into a fluid, and reused. Meanwhile, neither the extract itself nor the surrounding air (or ultimately the consumer) is contaminated by any potentially toxic chemical. The machinery required to run this procedure is rather specialized and not cheap, consisting of pricey high-pressure pumps and chambers. Part of the supercritical carbon-dioxide extraction process is called "winterizing," and it uses alcohol (ethanol) to remove chlorophyll and pigments from the extract. This also helps harvest terpenes.

Remember earlier when we looked at individual terpene compounds, I mentioned their variable boiling points. Additional winterization and separation phases that account for these temperatures are necessary to preserve terpenes for removal. In practical terms, this leverages what is a disadvantage in the ethanol extraction methods described earlier into a plus: their tendency to soak up unwanted compounds. As a post-processing step in supercritical CO_2 extraction, the ethanol is used as a cleanup procedure.

Concentrates have many names: tinctures, crumble, honey oil, sap, budder, wax, shatter, rosin, live resin, dabs, BHO, and hash. We have already discussed the latter. Most of the designations just refer to texture and are thus pretty self-descriptive. The main property of concentrates is (obviously) that they are concentrated. While bud potency varies between 10% and 25% THC, concentrates range from 50% to 85%. Inhaled by the inexperienced or unwary, these hypercharged extracts can be the cannabis equivalent of dynamite. But a benefit is that, while high-THC cannabis flower inevitably contains low amounts of CBD, concentrates can be blended to contain any proportion that's desired. If you would prefer a 50:50 ratio of THC to CBD, that's very straightforward to whip up. And if you like the flavor of particular terpenes, these can be added back into the concentrate during the blending process and are available to dispensary customers in the form of what's often referred to as "terp sauce," "full-spectrum hash oil," or "terp juice." Some consumers purchase high-THC concentrates and immerse them in a vial of terpenes before using them, a process known as "terp dipping." Terp juices and sauces by definition contain very high concentrations of added terpenes, combining THC potency with flavor intensity and perhaps entourage impact. Perusing Weedmaps website results for concentrates such as Dabblicious reveals a wide variety of choices.[42] In the world of live resins, there's a choice of Soul Safari, Tangie Pie, Golden Lemons, Peaches, or Super Glue, to name a few examples. Bottom line: the range of key ingredient choices is much greater for concentrates than for flower. Similarly, while flower can be smoked in a pipe or joint or vaporized, concentrates can be used by dabbing, ingested as an oil or tincture, or packed into a joint. Dabbing involves putting a small amount of the concentrate onto a heated nail and inhaling it (most often) through a bong-like glass apparatus; the nail can be heated with a crème-brûlée-style butane torch or a temperature-controlled electric coil (e-nail). Ingestible oils are by definition eaten like edibles, usually in capsule form, while tinctures are dropped under the tongue, where they are rapidly absorbed from the mucous membrane in the mouth with its many surface blood vessels. Inevitably some of the tincture is swallowed, following which it is metabolized in the same way as an edible. Some concentrates can be consumed using a vape pen or desktop vaporizer, for the latter by dripping them first on an absorbent pad.

Who uses concentrates and why? Young men who are heavy cannabis users favor concentrates.[43] Dabbers are generally regarded as being further along the consumption path that involves consuming larger quantities more frequently. But there are other considerations. Choice is one; as mentioned, a much wider variety

of cannabinoid percentages and ratios is available in concentrate form. Bang for the buck is another; if you're pursuing intoxication, then what you are really after is THC. And with concentrates, you're getting straight to the bottom line, even if a gram from a dispensary costs anywhere between $70 and $100. But if you purchase dabs in a state that taxes cannabis sales by weight, rather than THC content, that's a money saver.

Using a dab rig delivers a lungful of extremely concentrated nearly pure THC vapor that gets you really high really quickly. Setting the temperature high, say around 575°F–600°F, is apparently a recipe for the cannabis-user equivalent of being hit over the head with a sledgehammer or standard two-by-four, while setting the temperature a bit lower softens the blow somewhat. Common additional unwanted effects are coughing (especially if you scorch the product at too high a temperature), lethargy, mild nausea, and fleeting paranoia. Because the concentrations of THC are so high, choosing a precise dose is tricky and definitely a learned skill.

Inhaling such a large dose of THC, particularly if indulged in frequently, is likely a risk factor for both tolerance and cannabis use disorder. As noted in Chapters 6 and 7, high-THC-potency cannabis raises the risk for psychotic illness; use of concentrates is a concern in that regard, but no research has yet been published on this topic. Cannabis hyperemesis syndrome (repeated and severe bouts of vomiting) in the context of cannabis use is uncommon, affecting mostly long-term THC consumers. Using concentrates may be a risk factor in its development. Inhaling unwanted leftovers from the extraction process such as butane is known to be unhealthy. Scientists, including a group at Portland State University in Oregon are concerned that the high temperatures of dabbing degrade cannabis compounds themselves into potentially harmful chemicals such as benzene (a cancer risk) and methacrolein.[44] The Portland group used our old friend gas chromatography–mass spectrometry (GC-MS)—which we encountered in probing Shakesperean pipes, Chinese tombs, and biblical altars—to analyze the vaporized products of cannabis concentrates heated on a ceramic dab nail. Terpenes in the mixture, such as myrcene, degraded to produce worrisome, potentially toxic isoprene-related compounds at high temperatures.

In summary, when it comes to discussing cannabis, don't say "variety," say "chemovar." The ever-present urge for more and better intoxication, through concentrating key plant-derived chemicals, has led to new compounds, new practices such as dabbing, and perhaps new risks that are as yet poorly characterized. The cannabis plant contains multitudes of chemicals, each with its own pharmacologic effects. Its overall medicinal efficacy (as we shall see in the next chapter) may consist of more than the sum of those individual parts. Terpene compounds found in the plant represent a fascinating alternative window into both the medicinal and the intoxicating properties of the plant that deserve much deeper study.

* In contrast to other clonally propagated crops like apples and grapes, however, strain names are assigned to cannabis plants even if grown from seed. Thus, a cannabis strain name does not necessarily represent a genetically unique variety.

Chapter 9

MEDICAL MARIJUANA AND CLINICAL TRIALS

> In morbid states of the system, it [cannabis] has been found to produce sleep, to allay spasm, to compose nervous inquietude, and to relieve pain. . . . The complaints to which it has been specially recommended are neuralgia, gout, tetanus, hydrophobia, epidemic cholera, convulsions, chorea, hysteria, mental depression, insanity and uterine hemorrhage.
>
> G. B. WOOD AND F. BACHE, *The Dispensatory of the United States*, 1854[1]

> There really is no such thing as medical marijuana.
>
> US HEALTH AND HUMAN SERVICES SECRETARY ALEX AZAR, *Dayton Daily News*, 2018[2]

> Medical marijuana is used to treat a host of indications, a few of which have evidence to support treatment with MJ and many that do not.
>
> K. HILL, "Medical marijuana for treatment of chronic pain and other medical and psychiatric problems: a clinical review," 2015[3]

> You can't spell "healthcare" without "THC."
>
> ANONYMOUS

Cannabis has recorded medical uses dating back four thousand years, extending from ancient China all the way to the official *US Pharmacopeia* (at least up until 1942).[4] After a forty-plus year gap, the US Food and Drug Administration approved two synthetic analogues of THC for oral administration in 1985 and an oral form of CBD for treatment of childhood epilepsy in 2018. Whether these approvals represent the thin end of the wedge and a prelude to the much larger legalization of medical cannabis remains to be seen. Pondering this question from a scientific standpoint, some of the key questions are straightforward. What medical conditions might be appropriate for treatment with medical cannabis? Is there any convincing evidence of cannabis being effective for these conditions? And if so, at what doses, in which people, under what circumstances? Is cannabis safe to use, or does it lead to problems and side effects such as cannabis use disorder?

In this chapter, we first review the historical use of cannabis as a pharmaceutical and then examine some of the arguments for the use of "medical marijuana" and of its individual plant constituents. In addition, we survey the development of novel compounds not found in the cannabis plant but that similarly act on the endocannabinoid system. We also consider the numerous conceptual, practical, and legal difficulties that stand in the way of the necessary

definitive clinical trials that must pave the way for approval of cannabis-based medicines. Ultimately, only such investigations will tell us whether cannabis or its many constituents have utility for treating particular medical conditions. To help understand the current treatment landscape, we will review existing data regarding cannabis's effectiveness as a therapy for a variety of illnesses and try to gauge the strength of the supporting evidence for a handful of the best-studied ones.

This chapter does not attempt to review the detailed evidence for cannabis compounds as potential treatments for the long list of medical disorders where only pilot or small-scale clinical trials have been conducted. That endeavor is worthy of a completely separate stand-alone volume. Indeed, several such books and reports currently exist. (I would point readers to Michael Backes's *Cannabis Pharmacy: The Practical Guide to Medical Marijuana*, the 2017 revised and updated edition, as an especially informative example.)[5] Rather, I focus more on the scientific data and observations, and examine how investigators reached their conclusions. In other words, I try to show how informed, skeptical scientific thinking can best help us evaluate and scrutinize the available published evidence in order to help weigh the usefulness of medical cannabis and avoid the hype.

To get us started, and to illustrate how complex these issues are, I invite you to participate in an experiment of our own. Google a web page that gives an up-to-date, accurate list of all US states that have legalized the use of medical cannabis; then take a look at the qualifying conditions for which medical use has been deemed appropriate in each state. One source is the summary from the National Conference of State Legislatures at https://www.ncsl.org/health/state-medical-cannabis-laws.[6]

The first thing that will strike you is that these medical indications vary wildly from state to state, with little apparent consistency. A second obvious feature is that the qualifying conditions wander across the entire medical map and literally from head to toe. Conditions as diverse as seizures, post-traumatic stress disorder, inflammatory bowel disease, sleep disturbances, chronic pain, Parkinson's disease, anxiety, neurodegenerative disorders, migraine, multiple sclerosis, skin diseases, spinal-cord injury, traumatic brain injury, liver disease, glaucoma, fibromyalgia, and many others are all listed as suitable for treatment with medical cannabis in one or more states. Skeptics among you may ponder what could possibly explain how the substances contained within one plant can help treat such a diverse list of diseases. What underlying principle ties all these conditions together and renders them amenable to cannabis therapy? It's hard to imagine these illnesses share a common pathological mechanism that could be addressed by a single drug. But might they?

For many people, several possible explanations for the above observations leap to mind:

- The shotgun hypothesis: There are hundreds of potentially active substances within the cannabis plant; so, theoretically, different cannabinoids or terpenes, or different combinations of these agents, might help ameliorate a wide

spectrum of disorders.

- The-ECS-is-connected-to-everything hypothesis: the endocannabinoid system, with its widespread distribution in the body and its diverse, barely explored activities, may truly underlie a multitude of different disorders, so the cannabis plant could treat all of them by somehow acting on or regulating the ECS.
- The don't-worry-be-happy hypothesis: Cannabis helps many patients, in a very nonspecific and noncurative way, analogous to Valium, by making people feel less anxious about whatever disorder they have. Consequently, no matter what they are suffering from, they feel better after using cannabis. But their underlying medical problem is not addressed.
- The placebo-with-a-silver-lining hypothesis: Cannabis benefits from a strong placebo effect. People are helped because they have heard positive things about cannabis and believe the drug will benefit them. But perhaps beneath this phenomenon (and an enormous amount of hype), there exists a more modest number of medically related conditions in which cannabis or some ingredient thereof has a genuine therapeutic effect.

A journey through history

How can we decide which of these explanations best fits the facts and then extract the most valid explanation from these varied possibilities? One common-sense approach is to winnow through the historical record and find those conditions for which medicinal cannabis has been used consistently across the millennia and in different cultures. The area of overlap at the center of the resulting Venn diagram might provide useful leads. Another tack is to take a twenty-thousand-foot view of the best-designed and most carefully carried-out and controlled clinical trials of cannabis and its derivatives (particularly those studies that have used treatment randomization and placebo controls). Then we could attempt to derive some consensus on the conditions and circumstances where the drug is most beneficial. Using this latter approach, we can seek out the strongest empirical evidence and toss out what seems to be anecdotal, too preliminary to reach any conclusion, or attributable to placebo effects. This chapter attempts to survey all the above approaches.

A brief history of medical cannabis

As we explored in Chapter 3, as well as its utility as food, fiber, and intoxicant, the cannabis plant is a medicine of ancient lineage. Let's take a brief historical tour through cannabis therapeutics and see if we can find any commonalities in what conditions the drug has been used to treat over the millennia.

A caveat: for ancient medical use, it's helpful to separate medical from spiritual and ceremonial uses of cannabis, as these often are confounded. Such confusion is hardly unexpected. In the past, the origins of many medical diseases were obscure

and often believed to be located in the spiritual realm.

Hemp was first used in China 12,000 years ago, initially for its fiber and as a staple grain; its medical use evolved later. The Chinese documented that the female plant was most appropriate for medicinal use, and various descriptions of its preparation for such purposes can be traced back to around 4,700 years ago. Among other conditions, cannabis was used to treat gout and rheumatism, both illnesses involving pain and inflammation.

Ethan Russo has written a comprehensive historical account of medical cannabis.[7] He reviews the evidence for cannabis's use as a medicament as documented on ancient cuneiform clay tablets excavated from the Mesopotamian city of Nineveh (in present-day Iraq), dating to 2,600 years ago. These records reference and integrate medical knowledge from yet earlier Akkadian and Sumerian cultures, dating further back to 4,000 years before the present day. It's difficult to identify the herb that these records describe with certainty, and modern medical diagnoses do not align with those of antiquity. The fact that the plant in question is referred to both as a medicine and as being used in spinning and cable making, however, strongly suggests that cannabis is being specified. Its indications included use as a pain reliever and as treatment for muscle spasticity, kidney stones, lung congestion, depression, anxiety, and probable nocturnal epilepsy. As well, it was employed as a tonic and love potion for impotence.

Around 2,700 years ago, this near-eastern culture began to use a new term for cannabis: "kunubu," which sounds very much like the contemporary name for the plant. Cannabis was used in sacred rituals (including, as we saw earlier, in biblical Israel). Interestingly, "kunubu" was also used as a female personal name and as a term of endearment. I fully expect that such cannabis-themed girls' names will emerge in the next few years to replace the current Mary-Jane; stay tuned for Cannah Montana, Canndace, Cannabina, and Canna-Mae.

Ancient Egyptian medical papyri dating to over 3,500 years ago recommended cannabis for treatment of eye diseases and gynecologic disorders. At the same time, the plant was used as a source of fiber; hemp threads have been discovered in Egyptian tombs dating to over 3,300 years ago.

From China, cannabis ultimately made its way to ancient India, and ganja was considered one of the five key sacred plants in Vedic medicine. Around 3,600 years ago, the Atharva Veda recommended the herb "bhanga" to "release us from anxiety/grief," echoing Assyrian citations.[7] Later, by 300 to 400 AD, cannabis was well established in Ayurvedic medicine to treat a variety of conditions, including headaches, childbirth pain, epilepsy, and insomnia. A more recent medical use of cannabis was that of an inhalant to facilitate the birth process—a conclusion made from the discovery of a 1,600-year-old Israeli tomb containing the remains of a 14-year-old girl, who had died in childbirth, along with burned THC-containing cannabis.[8]

Based on pollen samples, cannabis has been used in sub-Saharan Africa for at least 2,000 years. When medical use began is uncertain, but termed "dagga" and brewed as a tea, the drug was again used as a pain reliever for both headaches and

childbirth.[7]

Around 1,200 years ago, cannabis reappears in the Middle East in medieval Arabic medicine, where it was used to treat nausea, epilepsy, pain, inflammation, and fevers. Close to 800 years ago, Moses Maimonides, the medieval Jewish physician and philosopher practicing in the Islamic world, included cannabis in his materia medica as "qinnab." He recommended its use as an anesthetic and to treat ear problems and colds. The plant arrived in Brazil nearly 500 years ago, along with the slave trade from Africa, and was used in folk medicine for relieving the pain of rheumatism and toothache. In 1758, the Frenchman Marcandier in his *Treatise on Hemp* referred to the use of the plant's root as a poultice for the treatment of arthritis and gout, and suggested its utility for treating "tumors." Cannabis roots harbor various terpenoids, sterols, and alkaloids but no cannabinoids.[7]

To summarize, these convergent traditional uses of medical marijuana include treating pain of various sorts, epilepsy, inflammation, insomnia, obstetric and gynecologic problems, and anxiety. These historical indications are rather consistent across cultures and unsurprisingly echo current recommendations for medical marijuana.

The modern European use of cannabis as medicine and intoxicant harks back to Napoleon's invasion of Egypt in the 1790s. His military forces were accompanied by an expedition of hundreds of historians and scientists, who excavated ancient sites, documented monuments, and discovered the Rosetta stone. The scientific team also wrote extensively regarding the cannabis they discovered was used there as both a medication and recreational drug. Alcohol was not readily available locally, so hashish became popular as a recreational substance among French troops. Disrespectful of local monuments, the Mamluks of Napoleon's Imperial Guard purportedly used the mighty Sphinx for cannonball practice, disfiguring its face. Although this turns out to be a myth, I have always imagined these polyglot troops as early 19th-century precursors of Hunter S. Thompson, wasted on some demoniacal brew of hashish and who knows what other intoxicants, firing their heavy-caliber weapons into desert targets. Enamored of its properties, French troops brought back cannabis to France. Paris quickly became the European epicenter for disseminating cannabis as a medicine. Hashish was soon used medically across continental Europe as a possible treatment for the plague as well as in psychiatric treatment (and as an intoxicant by the cultural and literary elite in France during the 1840s).

Contemporaneously, in the late 1830s the experiments of William Brooke O'Shaughnessy in Calcutta, India, suggested the usefulness of cannabis extracts in medicine. This Irish physician was a polymath and innovator who had earlier suggested the pioneering use of intravenous rehydration as a treatment for cholera. Outside of cannabis's medical use, he was also well aware of its intoxicant properties, describing how it produced "ecstatic happiness, the persuasion of high rank" (meaning, grandiosity) and "the sensation of flying, voracious appetite, and intense aphrodisiac desire." [9] This nicely captures the familiar "happy, hungry,

horny" properties of the drug. O'Shaughnessy published the results of his cannabis studies in prominent British scientific journals, and as a result of his influence, soon thereafter various cannabis extracts and tinctures began to be used for medicinal purposes in Europe and North America. On O'Shaughnessy's return to England in 1841, he brought cannabis herbal material and seeds with him and shared these samples with physicians throughout the United Kingdom. He experimented with cannabis for the treatment of tetanus, and he suggested that the drug had great promise in treating epilepsy and rheumatism. Interestingly, he noted that overtreatment with cannabis could lead to delirium. In an attempt to both stabilize and standardize cannabis for medical administration, he experimented with dissolving it in alcohol. The resulting tincture of Indian hemp developed in partnership with the pharmacist Peter Squire was known as Squire's Extract. A sample of this tincture from an antique still-sealed Victorian bottle was analyzed in 1984 using GC-MS (a technique familiar to us from Chapter 1). The extract contained traces of THC, the THC breakdown product cannabinol (which we encountered earlier), and significant amounts of cannabichromene.

Many of O'Shaughnessy's fellow medical practitioners became enthused by the prospect of cannabis as a treatment for a variety of disorders, and chemists attempted without success to extract the key curative chemical compound from it. Physicians back then had no inkling of the identity of either THC or CBD: science would have to wait a hundred years before these compounds were unmasked. Unlike opium, which could be easily converted into a standardized tincture (laudanum) that could then be dosed reasonably accurately, cannabis was problematic to pharmacists. It was difficult to standardize, quality control was elusive, and maintaining consistent accuracy in clinical dosing was especially challenging. Some patients responded nicely, while others became intoxicated or delirious, or failed to respond altogether. The Goldilocks dose proved elusive. All these pharmacologic roadblocks held back more extensive employment of cannabis as a medicine. Use finally ceased when the drug was outlawed in the United States and Europe in the mid-20th century. Over 50 years ago in the US, penalties for cannabis possession for any purpose were ramped up substantially by the Nixon administration with the declaration of the War on Drugs. Aimed primarily at stamping out recreational use, this decision simultaneously killed any hope for the development of cannabis-based medicines for over 40 years.

The tide begins to turn: physicians, patients, and politics

In the mid-1980s and early 1990s, interest in medical cannabis in the United States was reawakened from its prolonged couch lock for a variety of reasons. These included scientific discovery of the endocannabinoid system. This finding helped provide a scientific context for the drug's effect in the brain and elsewhere. While members of the counterculture reexplored the curative (and intoxicating) powers of the cannabis plant, chemists and pharmacologists began tinkering with synthetic cannabinoids. As we learned in Chapter 4, their laboratory discoveries ultimately

led to interest in intervening in the endocannabinoid system, initially through more straightforward CB receptor agonists and antagonists. Later, the scientists began developing drugs with more complex receptor effects, such as partial agonists and allosteric modulators. In addition, they began to manipulate the endocannabinoid system with drugs influencing its key enzymes such as FAAH. We will learn more about these efforts toward the end of this chapter.

A second influential factor in the rebirth of medical cannabis was a gradual alteration in public opinion that began to favor access to medical (as well as recreational) cannabis. Part of this rethink was due to persistent lobbying by organizations such as NORML. As well, there was a coming-of-age among members of the ’60s generation who were unimpressed by horror stories attached to the drug by their elders. A third factor pulling the weed bandwagon forward was long-standing anecdotal reporting of the plant’s medical benefits. In 1996, these combined forces led to California being the first state to legalize medical cannabis.

These currents of change culminated with the Institute of Medicine’s influential 1999 report recommending that cannabinoids might have a role in the treatment of pain, and movement and memory disorders.[10] This lengthy and thorough summarization also emphasized that risks could be associated with cannabis use. The institute’s major recommendations were to better evaluate physiological and psychological effects, individual health risks, and the role of various delivery systems, as well as to shorten clinical trials to determine the drug’s effectiveness in targeted conditions.

Opinions on use of the drug have now changed sufficiently that in a Gallup poll at the end of 2018, 66% of Americans surveyed expressed the opinion that cannabis should be legalized.[11] Since then, these numbers have increased further.[12] The federal government continues to resist moves in this direction, however. Despite the hopes and prayers of stoners and medical-cannabis advocates alike, no senior politician is willing to bite the brownie and take the initiative to de- or reschedule THC, or to legalize cannabis federally. Antimedical-cannabis forces are still strongly represented in government. For example, in 2018, Health and Human Services Secretary Alex Azar famously stated there was “no such thing as medical marijuana.” [2] Unfortunately, because of medical cannabis’s federal designation, the gravitational pull of public opinion has not yet translated into consistent federal or state medical regulations. Even in states that allow legal medical cannabis, employers can choose to fire workers for testing positive for THC metabolites on a drug screen. Medical facilities lack consistent policies regarding patient use of physician-certified medical cannabis. For example, when such patients are hospitalized, many facilities (again, even in states that have legalized medical cannabis) will not allow them to use their own drug supply during their hospital admission but instead prescribe alternatives such as opioids. Worse still, there are sad stories of individuals admitted to federally funded group homes who have had their CBD for epilepsy discontinued, provoking a return of their seizures.[13] Indisputably then, collectively in the US we have a regulatory

mess on our hands that requires consistent resolution at a federal level.

But the tide may be turning. In June 2018, following a 33-year gap dating from 1985 when the US Food and Drug Administration approved the use of two forms of synthetic THC, the agency approved Epidiolex. This purified, plant-derived pharmaceutical-grade CBD manufactured by Greenwich Biosciences of Carlsbad, California, was officially allowed for the medical treatment of certain forms of complex childhood epilepsy. The next year, the FDA held its first public hearing on regulation of CBD products.[14]

What are some common concerns about introducing medical cannabis?

Outside of the ill-informed and nihilistic "there is no such thing as medical marijuana" assertion, there are more reasonable concerns and objections. Some of them apply to the introduction of any new drug, while others are more cannabis specific. These issues include a variety of loosely linked topics. Let us examine these one at a time.

Lack of well-documented data on cannabis's medical benefits is the concern most frequently raised by the medical community. This can obviously be addressed by boosting the amount of good-quality medical-cannabis research. Of course, careful measurement of the drug's benefits needs to be accompanied by equally scrupulous assessment of unwanted effects. And to be thorough, we need to examine not only short-term efficacy but longer-term performance (does the drug continue to work over the long haul?) and the potential emergence of undesirable side effects with more chronic use. For example, healthcare providers worry about the gradual development of tolerance to the drug's beneficial effects, leading patients to escalate their doses over time. And higher doses of any drug increase the risk for greater numbers of unwanted effects. In the case of cannabis, these include delirium, anxiety, psychosis, reduced motivation, and muddied cognition, not to mention an increased potential for abuse and addiction. The latter concern arises from the observation that the cannabis use disorder rate for individuals using the drug daily is somewhere around 10%, so increased availability of medical cannabis might potentially create an unwanted and growing substance-abuse problem. There is at least some scientific basis to support that worry.[15] We know from PET brain-imaging studies that repeated cannabis exposure is accompanied by changes to brain CB_1 receptors in human subjects. The number of cannabinoid receptors becomes reduced significantly, and they are probably also less sensitive to the effects of cannabinoids. This observation is similar to that documented for brain nicotine receptors in cigarette smokers, where reduced receptor numbers are related to the intensity of tobacco craving.

Another topic is therapeutic trade-off. For example, in multiple sclerosis, relief of painful spasms may be obtained at the cost of worsened dementia. This type of problem is certainly not unique to medical treatment with cannabis, but it is an obvious concern in this case given the drug's cognitive side effects.

Safety data still need to be collected to answer other questions. Examples include the following: Are cannabis-based medications safe to administer to children, or to pregnant and lactating women? What is the risk of cannabis use disorder in populations at increased risk for this problem, such as individuals with chronic pain? And is it safe to use cannabis alongside opioid medicines? Let's take a closer look at this particular topic, which relates to the concept of harm reduction. If cannabis can help reduce opioid consumption (an issue discussed in Chapter 6), then implicitly we are trading one addiction (to opioids), which has a high morbidity and mortality rate, for a lesser but still nontrivial second use disorder. Part of what has to be balanced here is whether there are less harmful alternative but equally effective non-cannabis treatments. Understanding the risk-to-benefit ratio is important—in other words, quantifying the upside and the downside. In that manner, well-informed medical-care professionals can provide solid evidence-based guidance on these questions. An important area for future research is to study interactions of medical marijuana with opioid analgesics, examining issues of cross-tolerance, safety, and the trade-off between benefits and harms.

Secondhand smoke is an issue with tobacco smoking but is little studied for cannabis. If a pregnant woman is in a room, is it safe for her and her fetus if somebody is smoking medical cannabis in the vicinity? Diversion of the drug to nonmedical users, especially to vulnerable teenagers whose brains may be at particular risk of psychiatric and cognitive morbidity such as psychosis or perhaps drops in IQ, is an issue frequently brought up by concerned legislators and physicians. Or enterprising teens may filch Granny's supply of medical cannabis intended for her arthritis pain to attend to joints of a different nature.

Because cannabis is still illegal at a federal level, currently there is no standardized quality control for the drug. This problem applies to methods for analyzing and reporting percentages of cannabinoids and terpenes in medical and recreational cannabis, as well as ensuring an absence of potentially harmful contaminants such as pesticides, fungicides, fertilizers, mold, and heavy metals. FDA-based federal legislation could effectively deal with these issues. Another set of worries arises from the public-health sphere. Those concerns are that increased use of medical (as well as recreational) cannabis will result in increased numbers of marijuana-related motor-vehicle accidents and fatalities.

A final issue is that improperly labeled or packaged medical-cannabis products (such as THC-containing chocolate or gummies) will lead to inadvertent poisoning of children and household pets. An effective way to avoid this would be to institute standardized warnings regarding common health risks of THC, for example, as part of standardized safety rules for packaging (such as childproof containers).

Why are doctors confused about cannabis?

In addition to federal dithering, another factor holding back the legalization of

medicinal cannabis is pushback from the medical profession. What are some of the conceptual difficulties on the part of physicians that make it hard for them to wrap their heads around recommending the drug to their patients? I have some insight into this issue as one member of the Board of Physicians that advises the Connecticut Department of Public Health on which conditions may be appropriate for treatment with medical cannabis. I frequently talk with medical practitioners who for a variety of reasons find it very difficult to understand the concept of cannabis as a medical treatment. I will explain what they say puzzles them, but the primary point of confusion is not that the same compound can be used both as a recreational drug and as medical treatment. All physicians are familiar with the examples of opioids and cocaine in this context. Rather, the first perplexing issue for prescribers is that medical cannabis generally uses the entire plant (such as the flower) rather than one or more of its specific constituents (such as THC). I have already alluded to the fact that several other plant-derived drugs, such as morphine from opium poppies, are purified, plant-derived chemicals. But many physicians are aware that cannabis contains almost five hundred distinct chemicals in the form of cannabinoids, flavonoids, and terpenes. That mishmash, as well as complicated interactions among these compounds, perplexes them. As one of them confided in me, “I keep hearing about the concept of entourage effects, but I have a really hard time wrapping my head around the science behind that.”

Another problem is that medical doctors are used to prescribing standardized medications; 100 mg of this pure compound or 5 mg of that one. But many of them are acquainted with the highly variable and frequently changing percentages of THC and CBD available for purchase. Doctors favor precision. They are uncomfortable with this product variability, with the relative lack of standardized assays, and the absence of consistent monitoring of the drug for contaminants. When patients ask them which cannabis chemovar is most effective for treating a specific medical condition, they have no idea how to respond, largely because there are no reliable data to inform them. Even more perplexing to prescribers are recommendations on dosing. As one physician told me, “What do I tell my patients: take two bong hits and call me in the morning?” Because of the biphasic effects of cannabis, control of dose is extremely important. Using one quantity may improve a patient’s anxiety levels, but a larger quantity of the same cannabis will likely boost them. Naturally occurring individual compounds in cannabis occur not only in different proportions in different chemovars but may have opposite effects, say, on appetite. Allied with this chemical complexity is the fact that the drug is not being administered under medical oversight but by the patient themselves—in unclear quantities, using different methods and different products, and at uncertain intervals. Physicians are concerned about this, not only because of their lack of control over the proceedings, but also because it’s unclear what exactly their patient is taking.

Potential solutions to some of these problems are being worked on. For example, vaping devices currently under development deliver standardized concentrates in metered doses, whose use data for a particular patient can be

transmitted back by Wi-Fi to both the dispensary and the physician. If Mr. Smith tries three different chemovars for his back pain and anxiety over several months, the resulting data may be informative as to which compound, dose, and frequency best address his problems. But it's unclear in what form cannabis should best be administered for a particular condition. Should patients, for example, be using edibles, vaporizing their cannabis, or dropping tinctures of the sort familiar to O'Shaughnessy under their tongues? Is vaping bad for your lungs? Do the vagaries of gut absorption mean that your edible will suddenly kick in in the middle of the key presentation to your boss? While such uncertainties are potentially solvable pharmacologic problems, that does not imply they have been solved. Where promising findings of medical efficacy do exist, there's also no obvious way to extrapolate from studies on pure individual cannabinoids (for example, THC or CBD) to the complexity of herbal cannabis, or vice versa. Healthcare providers struggle with all these issues.

Another problem worth addressing is that there is frequent confounding among both physicians and members of the public regarding the legalization of medical versus recreational cannabis. Several states legalized medical cannabis before recreational. But the extremely wide range of health conditions for which the drug was permitted and the relatively cursory examination by a physician necessary to obtain a medical marijuana card—for example, in California—led many to suspect (not entirely unreasonably) that legislation represented a backdoor approach to legalizing recreational cannabis. An argument often heard in the physician community is that if legalization of medical cannabis represents a veiled step towards allowing access to recreational marijuana, then the best solution is to decriminalize all cannabis and leave the medical universe out of the process.

There is another set of issues that physicians tend to be less concerned about but probably should pay more attention to. Despite increasingly widespread use of both medical and recreational cannabis, many healthcare professionals do not routinely ask their patients if they are using the drug. Even fewer consider medical cannabis or CBD when deciding to explore new treatment alternatives. A number of them worry whether they can be sanctioned for recommending medicinal cannabis. In fact, they are protected by First Amendment rights, as instanced by a series of court cases. Also, due to lack of information and education, many physicians are unable to make recommendations regarding usefulness or dosage when patients solicit their advice on this matter. They are also unclear whether cannabis-related compounds interact with other medications they are already prescribing. There is some evidence of such interference for response to general anesthesia, recovery from surgery, and reaction to blood-thinning medication.[16,17] In large part, physicians' lack of knowledge on this topic also reflects the dearth of reliable research on these questions.[18]

It's not just physicians who are perplexed. We discussed the confusing federal situation a little earlier. Related conceptual problems exist at the state level too. For example, there has been remarkable inconsistency with implementation of medical-cannabis regulations to date from state to state. As we saw earlier in this

chapter, merely listing and comparing the medical and psychological conditions for which medical marijuana is allowed in the approximately 40 states that have passed such laws to date is educational. In some states, the list of approved medical diagnoses is as long as your arm, comprising a panoply of diverse disorders, for many of which there is little or no supporting research. Other states are much more restrictive in their listings but not necessarily more evidence based in their choices. Because there's no consistent federal approach to this issue, states are currently free to do as they wish. Indeed, they have implemented medical-cannabis legislation in an incredibly diverse and inconsistent manner. Many states have seized on cannabis legalization for medical or medical-plus-recreational purposes as a quick way to help solve their budget deficits, akin to legalizing gambling, by collecting "sin taxes." Unfortunately, in the case of medical cannabis, this means that more thought and planning has sometimes gone into crafting the sales and tax aspects of the legislation, with medical considerations being an afterthought. This has been true particularly when it comes to weighing evidence for and against inclusion of particular medical diagnoses. In turn, this lack of thoughtful planning is reflected in the confusion expressed by practicing physicians.

What stands in the way of clinical trials of cannabis as a medicine?

Another familiar refrain I hear from doctors interested in medical cannabis is "We never learned any of this in medical school. It's not in the textbooks. I'd be a lot more comfortable using this drug if the FDA did some decent clinical trials to provide me some direction in prescribing this stuff properly. But where are the evidence-based data?" So what's the proper answer to that last perfectly reasonable question? More generally, what is the gold standard to show that a drug works in order to get it approved at a federal level? Before approving a drug for any specific indication (for example, treating gout), the US Food and Drug Administration (FDA) requires evidence from two or more adequately statistically powered (usually construed as containing two hundred or more patients), randomized clinical trials. In other words, the study needs to contain sufficiently large numbers of patients to be convincing, with doses of the drug or placebo randomly assigned to minimize the powerful placebo effect that we discussed earlier. But the FDA currently officially designates cannabis as a Schedule I compound, meaning that it has a high potential for addiction and no currently accepted medical-treatment use in the United States. (Other Schedule I substances include heroin, fentanyl derivatives, LSD, ecstasy, and peyote.) So the obvious conclusion is that the federal authorities believe cannabis is unequivocally bad. But, as has been pointed out, in a move that seems to directly undermine this categorization, the US government itself holds US patent US6630507B1 for CBD. That application covers "pharmaceutical compounds and compositions that are useful as tissue protectants, such as neuro-protectants and cardio-protectants. The compounds and compositions may be used, for example, in the treatment of acute

ischemic neurological insults or chronic neurodegenerative diseases." [19] Obviously, this dual-faced approach (essentially, "We have classified the substance as a dangerous drug with no medical use, but we've also taken out a patent because it may be useful in treating strokes, heart attacks, and chronic neurologic illnesses,") makes no logical sense. Because of its current federal scheduling, proposing a clinical trial of cannabis or even one of its constituent cannabinoids quickly becomes ensnarled in a welter of federal bureaucratic regulations; what investigators in the field refer to as "green tape." It's not completely impossible to conduct such studies, but jumping through multiple time-consuming hoops is certainly a requirement and therefore a significant discouragement. Even the application process of obtaining placebo cannabis containing no THC or CBD whatever recently required my lab to submit more than a dozen documents and to wait several months before receiving the product. Thus far no federal administration has been willing to bite the bullet when it comes to rescheduling cannabis or its derivatives, although several 2020 presidential candidates supported such a move in principle. In late 2021 legislation was passed to try to make the approval process easier. To date, that has resulted in little noticeable benefit for researchers. Until recently, the National Institutes of Health was more focused on demonstrating problematic effects of cannabis and therefore much more likely to fund studies on psychosis or driving impairment, for example, than investigations aimed at demonstrating possible beneficial effects. This stance may well be appropriate for the National Institute on Drug Abuse, whose mission is to focus (of course) on drug abuse. But recently the NIH's National Center for Complementary and Integrative Health began funding grants to explore trials of cannabinoid compounds for pain.

In 2017, updating their 1999 recommendations, the National Academies of Sciences, Engineering, and Medicine published *The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research*. In the section "Challenges and Barriers in Conducting Cannabis Research," this report emphasized that despite the changes in both US state policies and cannabis use, the federal government "has not legalized cannabis, and continues to enforce restrictive policies and regulations on research into the health harms or benefits of cannabis products that are available to consumers in a majority of states." [20] So "green tape" is still a problem. It is true that the federal government has not significantly updated its restrictive policies regarding cannabis research in over 40 years—since the Nixon administration. The National Academies committee responsible for the report identified multiple barriers to research on cannabis and cannabinoid research. These included the necessity for any application to be reviewed by multiple federal and local agencies, and the rule that any substances must be obtained from the National Institute on Drug Abuse (NIDA). In practical terms that meant that until very recently cannabis for research purposes had to be obtained from a single provider at NIDA, sourced from the University of Mississippi, which grows smallish quantities of the plant material. This Magnolia State cannabis has been criticized for being both less potent than

and unrepresentative of the drug that can be obtained from any local dispensary. Its maximum THC content is low, and, rather than fat buds, the material resembles something old and long neglected that you might pull out of the back of your kitchen spice drawer. Research carried out with this cannabis therefore likely lacks necessary validity and generalizability. This situation may be changing slowly for both quantity and diversity of government-supplied plant material as new legislation kicks in. The issue of the low-THC content of NIDA-supplied cannabis can be compensated for experimentally by using a vaporizer loaded with sufficient weight of material to mimic a typical street dose, but many other problems remain.

For example, in 2019 researchers at the University of Northern Colorado performed genetic analyses on almost 50 different cannabis samples, including NIDA marijuana, non-THC-containing hemp, as well as various indica, sativa, and hybrid chemovars. In a research report published on the site bioRxiv, the authors demonstrated that nondrug hemp and THC-containing cannabis were genetically distinct strains.[21] That's not entirely unexpected. Rather shockingly, however, the NIDA drug samples shared a closer "genetic affinity with hemp samples in most analyses," compared to commercially available cannabis.[21] In a parallel to the old joke about airline food—the quality is low and the portions are too small—in response to criticisms regarding its low output and measly THC content, in 2019 the University of Mississippi agreed to boost its annual cannabis production for researchers. Several years ago, the federal government also agreed to make cannabis for experimental purposes available from a larger variety of suppliers, as opposed to the current single source. In practical terms, progress to solve those issues has been notably slow.

Non-flower formulations such as edibles and concentrates are also not yet available through NIDA, although this federal agency is moving slowly to become more responsive to such requests from clinical investigators. In 2015 spending by the National Institutes of Health on all cannabinoid research (including that in animals) totaled just over $111 million. The 2017 National Academies of Sciences, Engineering, and Medicine report concluded that "a diverse network of funders is needed to support cannabis and cannabinoid research that explores the harmful and beneficial health effects of cannabis use." [20] In an interview, Orrin Devinsky, director of New York University's Comprehensive Epilepsy Center, stated, "We have the federal government and the state governments driving a hundred miles an hour in the opposite direction when they should be coming together to obtain more scientific data. . . . It's like saying in 1960, 'We're not going to the moon because no one agrees how to get there.' " [13] But access to CBD for experimental purposes is likely to improve. In 2018, legislation removed hemp-derived products such as CBD from Schedule I status and allowed the cultivation of hemp, officially defined as having less than 0.3% THC content. Also in 2018, the Senate Agriculture Committee passed the 2018 Farm Bill that legalized the cultivation of non-THC-containing hemp and allowed its cultivation by universities. These provisions were backed by Senate Majority Leader Mitch McConnell of Kentucky, in part to help support farmers in his home state who

were concerned about lost revenue from falling demand for tobacco and were seeking alternative crops.

Cannabis researchers have their woes. For the consumer, potential problems are even worse. Even in states that have legalized medical cannabis, using cannabis products from a dispensary can still land an individual in a world of trouble. For example, because of the federal laws on cannabis, many companies that routinely test staff for drug use will still terminate employees for a positive THC urine test, even in the face of a valid medical-cannabis card. In addition, because of a lack of standardized testing, some individuals have purchased what they believe to be pure CBD oil only to discover it contains a sufficient amount of THC to show up as positive for the latter substance on their employment drug test. Conversely, employers worry about suboptimal performance from stoned or hung-over-from-cannabis employees in jobs that require sustained attention. There is some basis for their concerns. Legal or not, the number of cannabis consumers is growing steadily. Quest Diagnostics recently published a study showing that use has increased by 16% since 2014 to 2.8% of workers; almost 1% of individuals in safety-sensitive jobs, such as airline pilots and train operators, screened positive for THC.[22]

What might a well-designed clinical trial of cannabis look like?

Overall, what can we learn from the small number of medical-cannabis clinical trials that have successfully negotiated the above hurdles? We need to be informed by properly designed trials in order to move beyond the stage of anecdotes ("Medical marijuana helps my wife's neuralgia,") toward rational medical prescribing of cannabis-based drugs. So, what do we still need to discover before understanding marijuana's medical risks and benefits? The National Academies report discussed a little earlier stressed that proper study of the long- and short-term health outcomes of cannabis necessitated developing improved and better-standardized study methods. Why did they stress that point?

To be honest, in part because of all the restrictions and lack of funding, sadly there are design flaws in many existing medical-cannabis studies. Let's enumerate some of them. One problem is that many of the clinical trials are not properly randomized; who gets active medicine or placebo should be totally random. They should also be double-blind (to deal with expectation effects); neither the prescribing physician nor the patient should know exactly what they're prescribing or receiving, respectively. We've mentioned the placebo effect and the desirability of assigning some patients to placebo doses to help account for this. A related design issue is the need for subjects to be truly blind as to whether they are receiving active drug or not. It is pretty obvious to people participating in a cannabis trial when they are receiving placebo, because they will experience no psychoactive THC effect (unless they are part of a CBD-only study). Ideally, clinical-trial designers would insist on some form of "active placebo"—that is, a non-cannabinoid drug that had some psychoactive effect—so it would not be clear

to the participant whether he or she was receiving active cannabis or not. In a practical sense, this is difficult to arrange. For example, what substance should we choose for the active placebo? Are we sure that whatever drug we nominate for that purpose does not have its own medicinal effects?

How large a study sample should be is an issue that statisticians insist is extremely important. Ideally, placebo-controlled investigations with adequate sample sizes (around two hundred patients) are sufficiently powered to reach confident conclusions about a drug's usefulness, meaning that any effects observed are not just due to chance. Decently sized subject samples also enable clinicians to gauge how powerful a drug's effects actually are (what statisticians refer to as its "effect size").

Other important issues relate to making sure that you gather important information about your participants. Many studies do not adequately document the patients' other substance use, both legal (such as prescribed opioids) and illegal. This is important because, for example, a patient's pain may be masked partially by their opioid medication so that potential beneficial analgesic effects of cannabis are masked. To be properly informative, a well-designed trial also needs to report all relevant outcomes, both wanted and unwanted. For example, if cannabis is being prescribed for painful spasms resulting from multiple sclerosis, it's important to know not only whether pain was relieved but also whether there was worsening of preexisting cognitive impairment.

Professionals who conduct clinical trials for a living raise a number of other related questions. They want to know whether the sample studied was representative of the target population. For example, did the sample capture the typical age range of individuals affected by a particular disorder, and the usual proportion of men and women affected by the disease? Was it generalizable in the sense of including ethnic minorities, who may metabolize the drug differently? These clinicians are interested in whether the duration of the clinical trial was sufficiently long and whether the outcome measures were adequate to test the hypothesis. For example, if the experiment was testing the effectiveness of cannabis in treating ADHD in teenagers, were subjects asked only whether they felt they could concentrate better, or were college grades tracked to validate the outcome? In some of the published cannabis clinical trials, it's hard to determine what the primary outcome actually was, because it's never clearly stated. Another issue is against what standard the cannabis should be tested. Rather than just active drug versus placebo, there may be alternative existing FDA-approved treatments available against which the cannabis can be compared. Cannabis doesn't always meet this challenge. For example, in the case of glaucoma, it's less effective and has more side effects than available existing medical treatments.

Other design issues have complicated the head-to-head comparison of medical-cannabis trials. Some studies have employed whole plant marijuana, while others have used individual constituents such as THC or CBG. Other trials have used a wide variety of administration routes and substances (for example, smoked versus oral, versus vaporized THC or oral mucosal sprays). These different routes of

administration make it hard to compare drug effectiveness on a level playing field. For those readers interested in finding out more information regarding issues involved in designing quality clinical trials, they are listed at the following websites: GRADE working group[23] and BMJ Best Practice.[24]

Given these almost inevitable problems with many existing studies of medicinal cannabis, how can we weigh the evidence in the absence of rigorous clinical trials? The honest answer is that it's very difficult to come to any conclusion because of the conundrum of few conclusive clinical trials being feasible with an FDA Schedule I substance that by definition has no accepted medical use. The only effective way forward will be to have the federal government reschedule cannabis and its constituents, and to encourage the flourishing of well-conducted clinical trials. With all these caveats in mind, and not forgetting the many current barriers impeding quality research, let's look at what pharmacologists and clinicians have discovered to date and what the US government has approved for use.

What cannabis derivatives are already FDA approved?

A small number of THC and CBD products are already federally approved and prescribed by doctors. Some of these compounds are synthetic copies of THC, while others contain CBD or THC extracted from cannabis plants. The situation in the US differs from that in other countries. For example, while some nations allow the medical use of mixtures containing CBD plus THC, none of these mixtures are currently FDA approved in the US; hence they are unavailable. Bedrocan, for example, is a form of dried cannabis-flower extract containing THC and CBD in different ratios, approved and marketed in Europe. Nabiximols, marketed as Sativex, is a 50:50 THC-CBD oral spray, extracted from cannabis sativa plant material. Sativex is dispensed from precisely metered spray cannisters that provide a similar dose with each use. Such devices improve the accuracy of clinical trials in that patients can track how much of the medicine they are using. The product is sprayed inside the mouth or under the tongue, from whence it is fairly predictably absorbed. The drug was researched originally in the UK by GW Pharmaceuticals, which in 2021 was acquired by Jazz Pharmaceuticals, headquartered in Dublin, Ireland. Sativex is marketed legally in 15 countries, including Canada, Mexico, and parts of Europe, for treatment of painful spasticity and neuropathic pain in multiple sclerosis. It is not yet approved for use in the US.

Let's take a look at some of the cannabis-related medicines that are prescribed in the US. Starting with CBD, Epidiolex, another GW Pharma/Jazz product, received FDA fast-track development for treatment of two uncommon childhood epilepsy diagnoses (Dravet and Lennox-Gastaut syndromes). This drug is a purified, plant-derived form of pure CBD designed for oral administration. It proved remarkably effective in treating children with these often-devastating, traditionally hard-to-treat forms of seizure disorders. Success in carefully controlled clinical trials, combined with its very benign side-effect profile, led to

approval by the US FDA in June 2018, with subsequent approval in Europe. Another drug, pure CBD gel (Zygel), is currently in FDA phase 1 and 2 trials for several disorders.

Moving on to THC, there are currently many FDA-approved THC-only medications. Dronabinol (marketed as Marinol) is a form of synthetic (not plant-derived) THC in an oily base, administered in capsules. The drug is used as an appetite stimulant in patients with the AIDS wasting syndrome. Patients afflicted with this condition often have drastic losses of appetite and weight. The idea is that the drug stimulates appetite by giving patients "the munchies." Dronabinol is also approved for combating cancer-chemotherapy-induced nausea and vomiting. Dronabinol is the drug that we administered to research subjects at Johns Hopkins in our time-estimation study referred to in Chapter 5. For unclear reasons, patients taking dronabinol typically do not report a cannabis-induced "high" such as they might experience from edibles, nor do they seem inclined to abuse the medication. Nabilone (marketed as Cesamet and Canemes) is another FDA-approved THC analog available in capsule form for treatment of nausea in cancer-chemotherapy patients. A third form of orally administered THC approved in the United States is a solution, marketed as Syndros, for similar indications. A significant problem with all these oral preparations is unpredictable absorption from the gut. The bottom line is that at present the number of cannabinoid medicines available for prescription in the US is rather small, and the current range of clinical indications is very restricted. No whole-plant extract of cannabis or THC-CBD mixture is approved, and neither is any herbal form of the drug.

Cannabis as a pain reliever

Despite the regulatory restrictions, cannabis is used informally to treat a huge array of problems. Here, we will focus on only one, chronic pain, because it's one of the better studied (relatively speaking) indications and associated with several important public-policy issues. In the US, the majority of medical-cannabis users state that chronic pain of one sort or another is their indication for the drug. The country is currently undergoing an opioid crisis due to addictions that often begin with medically prescribed opioid drugs, given to patients as analgesics for acute and chronic pain. While opioids are ideal for short-term management of acute pain, they are (despite pharmaceutical-company propaganda) now regarded as inappropriate to treat the vast majority of chronic-pain cases. About 25% of individuals prescribed opioids for chronic pain misuse them, and around 10% develop an opioid use disorder. By 2017, 1.7 million Americans had a substance use disorder stemming from prescribed opioids, and both intentional and unintentional opioid-related deaths, numbering around fifty thousand a year, were snowballing into a major public-health crisis.[25] As pain patients became tolerant to opioids, and physicians were sanctioned for overprescribing these drugs, cheap fentanyl—an extraordinarily powerful opioid and potentially lethal drug—began flooding the illicit drug market, greatly exacerbating this preexisting problem.

As we reviewed earlier, cannabis has been used since ancient times for pain relief. From the earlier example of Jo Cameron,[26,27] we see that the ECS appears important in pain control. So the obvious question is whether cannabis is an appropriate substitute for opioids in terms of harm reduction; meaning, can we substitute a potentially very harmful class of drugs (opioids) with a less damaging one in the hopes of reducing opioid-related morbidity and mortality? Answering that question turns out to be quite complicated.

First, some background. Although the answer to this next question seems intuitively obvious, it's worth asking: what exactly is pain? After all, it's not a quality "out there" in the world, such as heat, light, or sound. Pain is conventionally defined as "an unpleasant, sensory-emotional experience, associated with actual or potential tissue damage." [28] While acute pain signals damage to body and acts as an alarm and protective system, chronic pain is an umbrella for many diverse phenomena. A syndrome with many causes, and not a distinct disease, chronic pain is common, affecting 50 to 100 million US adults. It is often described as pain that lingers after the acute cause (such as injury) has resolved. Defined more precisely as persistent physical pain lasting longer than three months, while causing significant distress or loss of function, it is often accompanied by disability, emotional disturbance (including depression and suicide risk), and social withdrawal. Whatever its causes, pain in general is responsible for about half of US physician visits, and chronic pain in particular is expensive. Its annual costs are estimated to be about 3% of GDP. These sizable economic effects are a result of a combination of increased medical-resource use plus billions of dollars in lost productivity. Cancer pain is considered a separate entity of chronic pain as its cause is often obvious (for example, invasion of nerves by a tumor).[28]

Here's how pain works. Specialized pain-sensing neurons exist whose cell bodies (think back to Chapter 4) are located in dorsal (the back of the body) root (places where nerve bundles emerge from the spinal cord) ganglia (collections of nerve cells) found all the way up and down our spinal column. These dorsal root ganglia neurons send nerve fibers from their cell bodies "outside" to our skin and "inside" to our internal organs such as the gut. One notable place that's not supplied with any pain fibers is the brain itself. Poking a brain exposed at surgery in an awake patient elicits no pain. Pain fibers are tipped with specialized receptors sensitive to different types of stimuli, including sharpness, heat, pressure, and chemicals released by tissue damage, as well as to irritant compounds like acids and capsaicin in chili peppers. As a representative example, chemical pain receptors are sensitive to signals triggered by injury, inflammation, or irritation. When thus provoked, they relay a signal representing pain through the specialized fibers back to the cell bodies that are assembled in the dorsal root ganglia, and from there up the spinal cord and into a signaling switchboard in the brain called the thalamus. The thalamus relays pain signals up to the brain's sensory cortex, where they are perceived consciously as pain. This portion of cortex generates signals that travel back down through motor pathways. In turn,

the signals mediate behaviors such as cursing loudly or pulling your hand out of a flame.

Just as our bodies have an ECS and a variety of endogenous cannabinoid compounds, we also have an endogenous opioid system and a corresponding collection of endogenous opioids. Under normal circumstances, pain signals are tamped down by such endogenous opioid compounds (for example endorphins) that act on specialized opioid receptors (mu and kappa subtypes) scattered throughout the human nervous system. Those receptors are located specifically in many of the locations we've just mentioned. These include neurons of the dorsal root ganglia, the pain pathways of the spinal cord, and parts of the midbrain. From there, they modulate pain signals. What's fascinating, and certainly relevant to our story, is that pretty much every place that opioid receptors are located, parts of the endocannabinoid system are right there hanging out with them. This predictable co-localization strongly suggests that the ECS has a normal physiological role in controlling pain.

There are many other reasons to think that's the case. First, there's Ms. Cameron, the Scottish woman we met in Chapter 4, with her two separate ECS gene mutations rendering her virtually free from sensations of both chronic pain (her hip) and acute pain (childbirth and her hot iron).[26,27] Second, the "extended" ECS also includes TRPV1 and GPR55 receptors. The former are found mainly inside pain-sensing neurons in the peripheral nervous system, where they sense heat.[29] (They are also located in the brain, where their function is to regulate body temperature.) Capsaicin, the substance that makes chili peppers "hot," binds highly specifically to these peripheral TRPV1 receptors (for example, on our tongue) and causes them to transmit pain signals. GPR55 receptors process pain and inflammation stimuli, and are distributed throughout sensory integration sites next to the spinal cord and in the gut.[30–32] They also occur in the brain, where their role is more obscure. Third, injured tissues release endocannabinoids (2-AG and anandamide) that target CB_1 receptors located in the brain, dorsal root ganglia, and spinal cord, and target CB_2 receptors in peripheral tissues.[33,34] Fourth, we have noted that cannabinoid receptors sit cheek by jowl with mu opioid receptors in all these major nervous-system pain-control areas.[35–37] As well as providing binding sites for endogenous pain-controlling opioid compounds such as endorphins, opioid receptors are the docking stations for pain-relieving opioid drugs such as morphine, heroin, and OxyContin.[38] If frequent proximity strongly suggests the ECS and opioid system work hand in hand to control pain, further evidence intimates that their relationship is even closer.[39] Cannabinoid and opioid receptors can actually fuse together (hybridize) to produce functional receptors that control pain.[40] And CB_2 receptors outside the central nervous system likely modulate pain not only by inhibiting inflammatory responses but also more surprisingly by encouraging release of endogenous opioid peptides. So the two endogenous neurotransmitter systems are not just hanging out together; they seem to be able to trade places and to cooperate in pain control. Finally, regular cannabis smokers hospitalized for routine surgery and cut off from their drug experience some form

of pain-sensitivity rebound. They often need additional pain-control medications (such as opioids) after surgery. The situation is analogous to individuals whose opioid supplies are discontinued.[37,41,42]

By now, we are very familiar with the underlying mechanisms by which client cannabinoids influence the ECS. THC is a CB_1 receptor partial agonist that also binds to GPR55. CBD is a noncompetitive allosteric modulator of CB_1 receptors but likely an allosteric modulator at mu opioid receptors, a TRPV1 receptor agonist, binds to $5\text{-}HT_{1A}$ receptors, and has anti-inflammatory, antioxidant, and immunosuppressive effects. The less well-known cannabis constituent, the cannabinoid tetrahydrocannabivarin (THCV), is not notably psychoactive, although it is prominent in some chemovars such as Tangie and Durban Poison. Like CBD, it has analgesic and anti-inflammatory properties but in addition has complex effects at both CB_1 and CB_2 receptors. THCV is an effective pain-relieving compound in mice, but it has been little explored clinically in humans.[43]

Showing that the ECS and its components are very likely involved in day-to-day pain control is different from saying that plant cannabinoid compounds, whose effects are mediated through the ECS, are effective in pain control. So let's examine that evidence.

Pain research is tricky. Studying how effective any drug actually is as an analgesic is a topic with its own particular set of prickly problems. First of all, pain is an inherently subjective, private experience. It's not possible for researchers to stick a theoretical "painometer" into a patient and obtain an objective, reliable readout of the sufferer's pain level. As we've seen, acute and chronic pain are different entities requiring different treatments. And chronic pain can arise from a multitude of causes that may require different therapeutic approaches. A clinician colleague of mine once complained that "the term 'low back pain' is about as specific and useful as saying 'low front pain.' " Cannabis could be helpful for some forms of chronic pain but not others, depending on cause and location. These practical difficulties have not deterred a number of states, including California and Iowa, from designating chronic pain alone as a qualifying condition for their medical-cannabis laws.

Thus, in cannabis studies focused on pain relief, the most informative data comes not only when patients can tell their healthcare provider, "I have less back pain," but also when there are adequate comprehensive outcome measures. Example would include a reduction in opioid use or a return to work—in addition to the patients' subjective pain reports. Documenting the underlying medical condition provoking the pain is also useful. For example, cannabis may be helpful for chronic pain caused by diabetic nerve damage but ineffective for treating cancer pain. Another missing design feature in many analgesic trials is the long-term follow-up of study subjects to assess both efficacy over the long haul and the possible development of later-emerging problematic or adverse side effects. These include tolerance, addiction, and the development of psychosis symptoms. These are potential problems because there's epidemiologic evidence that chronic pain is a significant risk factor for cannabinoid dependence. There are yet other factors

complicating pain-and-cannabis research. We need to distinguish between primary pain relief versus intoxicant effects on mood and consciousness that may be altering pain perception only secondarily—in other words, the notion that "my pain is still there, but I'm high, so I don't care about it as much." Not that such an effect would be inherently unhelpful, but we would need to distinguish between the two sets of circumstances.

Research studies themselves are often not well designed. Cannabis is federally illegal, discouraging performance of large-scale clinical trials. Most often, patient numbers are few and studies not conducted across multiple centers. Few clinical trials are double-blind and placebo-controlled, a prerequisite for judging whether a drug is truly clinically effective. Even then, deciding which placebo to provide is also challenging. If there are no psychoactive effects, patients can often guess accurately what compound they are likely receiving. Given those restrictions, many conclusions regarding how effective cannabis is in relieving pain have had to settle for the (inadequate) data available. Thus, they have often lumped together reports for medical- and recreational-cannabis users and disparate acute- and chronic-pain syndromes; and they have included cannabis at a wide range of doses, derived from different formulations or administration methods (or pure synthetic THC medical preparations such as dronabinol versus tinctures, flower, edibles, and CBD oil with varied THC-to-CBD ratios), and obtained from different sources (multiple dispensaries, etc.).

Given all the above, what does the existing limited research actually tell us? My usual go-to for answers is meta-analyses of randomized, controlled trials, because these try to examine large numbers of similar studies on a level playing field to reach generalized conclusions about what's going on. That's tough in this situation because if good-quality data are not available as your input, then the output has to be viewed with suspicion. Nevertheless, here's an overview of those meta-analyses.

One study examined 28 randomized trials of 2,454 patients suffering from both acute and chronic pain (the latter mostly due to nerve damage). The analysis showed that, compared to placebo, cannabinoids were associated with greater pain reduction in chronic pain patients—but not in a way that seemed dose related. Acute pain was lowered by medium cannabis doses, but higher doses actually increased pain.[44] Another large-scale review and meta-analysis included all available randomized, controlled trials for both chronic and postoperative acute pain management.[45,46] Of 43 such trials, about half were suitable for analysis. These showed more limited evidence for more pain reduction in chronic pain, particularly when cannabis was inhaled, but many studies showed no effects at all. Adverse effects included anxiety, unsteadiness, dizziness, clumsiness, delirium, sleepiness, falls, feeling intoxicated, impaired memory and attention, and abdominal discomfort. Unsurprisingly, older, chronically ill, and heavy users experienced the most side effects. Treaters were concerned about patients' risk for motor-vehicle accidents. Other subsequent meta-analyses show broadly similar results. For example, Johal examined 36 trials subsuming more than 4,000

patients. The study concluded there was “moderate” evidence of pain reduction by medical cannabis compared to placebo in non-cancer-chronic-pain patients. Typical of published meta-analyses on cannabis, the drop in visual-analog pain scores on a 0- to 10-point scale was unimpressive, at less than 1 point. Peak relief occurred between two weeks and two months. Medical cannabis was less effective for multiple-sclerosis pain than for chronic nerve damage (neuropathy).[47]

To summarize these studies, the level of evidence for pain relief was generally low to moderate, in large part for the reasons we reviewed earlier. Bottom line: the results leave a lot to be desired when it comes to overall scientific validity, and evidence is limited. Pain conditions, drug doses and routes of administration, and length of follow-up varied widely (for example, some patients were given various forms of medical-grade cannabis, and others were not, so it was hard to compare equivalent doses). Large swaths of the safety data derived from recreational use. Many studies were small in scope, and pharmaceutical companies often were unable to provide necessary data. Mean pain scores were certainly lower in cannabis-treated patients compared to placebo; but, although significant across large numbers of patients, in general these reductions were modest in degree. The incidence of serious side effects was rare. How cannabis was administered (pills, tinctures, or inhaled) didn’t seem to make much of a difference to efficacy, although these methods were not compared directly. There are some suggestions that cannabis was especially helpful in alleviating neuropathy pain. Products with more balanced THC to CBD ratios approximating 1:1, particularly in the form of sublingual sprays, were associated with small improvements in pain relief and overall function, together with increased risk for sleepiness and dizziness. Bumping up the ratio of THC was associated with better pain relief but more side effects.[36,48–51]

One thorough study of this issue reached what I believe is an accurate final conclusion: “Studies in this field have unclear or high risk of bias and outcomes had . . . ratings of low- or very low-quality evidence. We have little confidence in the estimates of effect. The evidence neither supports nor refutes claims of efficacy and safety for cannabinoids, cannabis or cannabis-based medicines in the management of pain.” [52] Similar conclusions have been reached by other critical reviews.[53] A huge and mostly unexplored issue concerns the bell-shaped dose-response curve of many subjective effects of cannabis, where large doses of cannabinoids can result in completely opposite effects than lower ones. Future clinical trials will need to document doses (and preferably even blood levels of drug) extremely carefully.

Recently, based on the same evidence, other researchers concluded that cannabis products are not much better than placebo in relieving chronic pain.[54] Their meta-analysis, which received widespread media coverage, emphasized that positive media attention boosts patients’ expectations and reinforces their belief that cannabis will help them. Thus in non-placebo-controlled trials, this bias risks becoming a self-fulfilling prophecy. Given the low quality of available evidence, I believe that this claim is premature. At the risk of being repetitious, I’ll add that

the only way we can reach any definitive conclusions is to conduct the necessary large-scale properly controlled studies that have yet to be carried out.

Now that we have looked at clinical trials of cannabis (which we emphasize is certainly not one entity), what do we know regarding the usefulness of individual plant constituents in treatment of pain (which is also more than one essence)?

Does using cannabis for pain raise the risk of cannabis use disorder?

A handful of studies suggest that chronic-pain patients who use cannabis have an increased risk of abuse liability,[55,56] in agreement with epidemiologic studies.[57] If that's the case, some useful suggestions for reducing the risk of cannabis use disorder include balancing THC-to-CBD ratios, starting with low drug doses, and raising doses slowly and cautiously. In addition, screening potential patients for those with previous substance use disorders and heavy current recreational cannabis use, monitoring use carefully, and balancing the patients' need against the potential for harm are all important factors.[58]

Does using cannabis for pain lower the risk of opioid use disorder?

This super-important, hotly debated issue is important to resolve, because if cannabis can substitute for opioids and provide a less harmful alternative for pain control, then it can potentially save lives and help mitigate the dire effects of the current opioid epidemic. There are several embedded questions here. Can cannabis be completely substituted for opioid pain medicines, and if so, does this reduce risks for opioid withdrawal? Or is it possible instead to take cannabis and opioids simultaneously, thereby leading to a significant reduction in opioid doses? If the answer to these questions is yes, then will such substitution and harm-reduction strategies lead to reduced numbers of opioid overdoses and deaths? Or if these strategies are ineffective, will there be a confluence of bad effects with pain patients suffering the downside of both medication types? Logically, that would result in a nasty combination of opioid use disorder and cannabis use disorder. These intertwined issues have been hard to resolve. Some review studies (for example, Okusanya's work in 2020)[59] report about a two-thirds reduction in opioid dosage when used in combination with medical cannabis in non-cancer chronic pain. The authors cautioned about both the weak design of currently available studies and the unknown optimal cannabis doses to achieve opioid reductions. Many patients assume that effective pain-relieving doses are equivalent to those needed to get "high." But there is little to support that contention, and pain-relieving doses may in fact be considerably lower than intoxicating ones.

A survey of two hundred illicit opioid users found that over half used cannabis to reduce opioid cravings, a strategy they claimed was effective.[60] A separate epidemiologic study in New York state, published by the American Medical Association, found that chronic-pain patients enrolled in the state's medical-

cannabis program who used medical marijuana for longer than a month were able to significantly reduce their doses of prescribed opioids.[61] Nevertheless, doubts persist. Earlier longitudinal analyses from the large National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) demonstrated that cannabis use was associated with higher incidence of both opioid use disorder and nonmedical use of prescription opioids. And unsurprisingly, given the increased risk for substance use disorders in chronic-pain patients, such individuals who use cannabis seem to have higher rates of substance use disorders. Not only that, but they do not seem to necessarily reduce their use of daily prescription opioids.[62–64] In summary, these seem to be early days in terms of access to hard persuasive evidence, but there are some optimistic signals. Certainly, there is a real need for well-designed studies to answer these extremely important questions. Such studies are often more definitive when they can track large numbers of individual patients treated by clinicians. These investigations can probe more deeply than examining epidemiologic trends across populations.

CBD, THC, and pain

Peripheral CB_1 cannabinoid receptors sit cheek by jowl with specialized pain-sensing peripheral receptors.[65] This proximity suggests a basis for physiological interaction. Peripheral cannabinoid receptors appear to be implicated in THC's effects on muscular and other types of pain.[66]

CBD as an isolated cannabis constituent may hold promise as a pain reliever.[67] As we have explored, there are several mechanisms by which it may accomplish this. A notable one is that CBD is an allosteric modulator of mu opioid receptors.[68] It also reduces inflammation and has effects on the immune system. This combination of activities may underlie some of CBD's pain-relieving properties, as demonstrated in mainly animal but also a small number of human clinical trials. In addition, recent rat models of neuropathic pain revealed that repeated low-dose CBD treatment induced pain relief predominantly through TRPV1 activation, reduced pain-related anxiety through $5\text{-}HT_{1A}$ receptor activation, and rescued impaired 5-HT neurotransmission.[35] Among the phytocannabinoids, CBD is joined by THC as a pain reliever. So, along with other effects of the drug, in what seems to be a consistent theme for CBD, pain reduction may also be contributed to by multiple simultaneous effects.

Earlier we encountered the terpene compound beta-caryophylline (BCP). Briefly, this is a non-cannabinoid molecule synthesized by cannabis plants (as well as other flora, including black pepper) that holds promise as a treatment for chronic pain. Initial experimental results mainly derive from BCP given to laboratory rats and mice. Because the compound is so fat-soluble, it quickly crosses from the blood to the brain. BCP is especially interesting as a potential medicine for humans because, at least in animals, it very effectively reduces both acute- and chronic-pain sensation as well as an experimental form of neuropathic pain that results from creating long-term nerve damage in the laboratory. BCP is a

potent peripheral pain reliever and anti-inflammatory drug in mice and rats. It has effects when administered orally, with behavioral responses within an hour of administration. It shows promise as a potential therapeutic compound for painful inflammatory conditions and autoimmune disorders. BCP binds directly to peripheral CB_2 cannabinoid receptors, where it acts as an agonist.[67] Some evidence suggests that caryophyllene's pain-reducing effects require participation of both the opioid and endocannabinoid systems. It is not clear whether this effect persists in the presence of other terpenes and cannabinoids commonly found in cannabis. BCP is safe to administer to humans and has Generally Recognized As Safe status with the US Food and Drug Administration, meaning it is approved for use as an additive to foods and pharmaceuticals.

In conclusion, a substantial number of rat and mouse studies support BCP as an effective pain reliever. There have been no such studies of BCP yet in humans, however, and no one has studied effects of very high doses in people. As a result, some laboratories, including my own, have begun thinking seriously about exploring BCP as a safe pain reliever in humans.

The CBD story continued: the good, the bad, and the ugly

It's fair to say that the mode of action of CBD and its effects are less understood than those of its fellow cannabinoid THC. So I apologize in advance for the fact that many of the paragraphs below will end by concluding something along the lines of "This medical application of CBD sounds promising, but there is too little evidence at this point to make any strong claim." With that in mind, first let's explore the well-documented, evidence-supported "good" side of CBD.

We've seen that cannabis has been used for centuries to treat seizures. Recently, double-blind clinical trials in hundreds of children across multiple centers compared placebo to standardized CBD preparations administered by mouth. These trials showed that the drug can be dramatically effective in reducing the frequency of seizures for certain rare, severe, early-onset, intractable childhood epilepsies. These conditions (such as Dravet and Lennox-Gastaut syndromes) account for a small number (less than 10%) of all childhood epilepsy, but they are often dire and have a disproportionate impact. Parents of kids with these conditions often feel helpless as their child suffers multiple different types of seizures in a day. These are often associated with delayed developmental milestones, falls in IQ, continuous seizure states that lead to emergency-room visits and hospitalizations, brain damage, and an almost 15-times increased risk of sudden death. Until recently there were no truly effective treatments for these individuals. Affected children were most often placed on multiple antiseizure medications, often resulting in marked sedation and other side effects, without much benefit in terms of seizure reduction.

In 2018, following rigorous large-scale and well-controlled clinical trials, the drug Epidiolex (purified CBD derived from cannabis plants) was approved for treatment of three intractable childhood seizure disorders by the US Food and

Drug Administration.[69,70] At the very high oral doses prescribed for these conditions (usually exceeding a gram per day), CBD side effects, when they occurred, were relatively mild: gastrointestinal disturbances, mild to moderate sleep disturbances, and increased liver enzymes. CBD was very effective against a broad variety of different types of seizures. Over 15% of kids treated were completely seizure free, and many caregivers reported that cognitive functioning, emotional health, and language and communication improved with CBD, whereas seizure-related injuries, hospitalizations, and emergency-room visits fell by about half.[71] A fascinating account of CBD's effectiveness in treating these seizure conditions was the cover story in a 2019 *New York Times Magazine* article by Moises Velasquez-Manoff.[70]

How is CBD causing these dramatic improvements? The short answer is we really don't know. Recall that cannabis has been used for centuries to treat epilepsy. Unlike THC, whose mechanisms of action are fairly well understood, with CBD we are more or less in the dark. CBD is pharmacologically promiscuous, and we are unsure which of its many documented molecular effects (if any) is responsible for its antiseizure activity, although many seem plausible. Harking back to Chapter 4, remember that CBD binds but weakly to endocannabinoid receptors. (It may be a weak negative allosteric modulator at CB_1 receptors.) CBD has calming effects on calcium release, reduces sodium currents within cells and sodium channels, and also reduces hyperexcitability at certain potassium channels. Any or all these effects on ions might conceivably calm epileptic mechanisms, but scientists aren't sure. Other possible beneficial CBD effects on seizures might stem from the drug's action on $GABA_A$ receptors or other mechanisms we touched on in Chapter 4, including G protein-coupled receptor 55 (GPR55) or the transient receptor potential vanilloid 1 (TRPV1) receptor. For example, GPR55 receptors influence glutamate release. Glutamate is an excitatory neurotransmitter. So calming its receptors, as CBD does, reduces excitation of brain cells. Overexcitation by glutamate in animal models can both trigger seizures and kill brain cells through overexertion. Basically, they are stimulated to death and die of exhaustion. Outside of the three severe childhood epilepsy syndromes, we are still in the dark regarding CBD's potential to manage additional treatment-resistant forms of epilepsy that occur in adults.

At a federal level, CBD extracted from cannabis plants was until recently a Schedule I drug, making it illegal. Epidiolex changed that landscape. The drug was federally de-scheduled, so CBD in that form is no longer a controlled substance. Those considerations do not apply to the type of non-FDA-approved CBD products sold in dispensaries or health-food stores. Nor does this rescheduling apply to THC.

Outside of treating epilepsy, what else can CBD do? One very common claim is that CBD modulates or offsets unwanted effects of THC, for example by reducing the risk for psychosis, lowering the potential for anxiety, and thereby mitigating risks from cannabis use disorder. In other words, cannabidiol makes cannabis "safer," acting as a kind of calming yin to THC's buzzy yang. These

claims have become almost an article of faith, but remaining ever skeptical, let's examine the evidence for them. The most carefully conducted laboratory studies giving healthy subjects THC and CBD in different ratios at doses commonly seen in medical and recreational cannabis fail to show that increasing the ratio of CBD to THC has any significant acute effect on driving safety. Nor does CBD modulate THC's detrimental effects on multiple measures of cognition, such as memory and attention, or on psychotic symptoms, such as paranoia or hallucinations (see for example Englund's work from 2023[72]). Similar studies also failed to show that CBD reduced the THC-induced "high" or its resulting pleasurable effects, for example demonstrated by how subjects rated eating chocolate. CBD also has no measurable consequences on THC blood levels. A recent small study administered "brownies" containing THC with and without CBD to volunteers. Surprisingly, this showed that adding CBD to the THC resulted in a stronger subjective "high," plus more cognitive impairment, anxiety, sedation, and speeding up of heart rate. One possible explanation for these counterintuitive results is that CBD is interfering with THC metabolism.[73]

A more prosaic explanation of CBD's claims to reduce THC's effects is that (as we saw in Chapter 3) cannabis plants bred for high THC content necessarily have smaller amounts of CBD. So plant cannabis with higher CBD ratios contains lower amounts of THC. To be fair, the above studies were all carried out in healthy populations under acute dosing conditions. Whether the same considerations apply to patient populations taking cannabis repeatedly over long periods is an important issue crying out for careful investigation.[74]

More promising is the notion that, since CBD has antioxidant and anti-inflammatory properties, it may be neuroprotective (for example by preventing damage to neurons that may be affected by trauma or too low a concentration of oxygen). In addition, CBD may hold promise as a general pain-relieving and anti-inflammatory drug[36,37,45,75] through a variety of mechanisms.[35] Overall, there is too little evidence yet to make any firm pronouncements here.

We previously discussed the utility of CBD as a potential add-on treatment for schizophrenia. Here too, conclusions as to the drug's antipsychotic efficacy are mixed, with two well-conducted recent studies from different groups coming to opposite conclusions.[40,76] It's fair to say that this issue of CBD's usefulness in treating schizophrenia remains currently undecided. One recently touted possibility is that CBD treats only certain biologically defined subtypes of psychotic illness.[77]

CBD also has probable antianxiety properties, although as mentioned better-powered clinical trials are needed to nail this down. Some early studies of acute effects in healthy individuals have been disappointing (see, for example, the work from Bloomfield's team in 2022[78]), but again large-scale more chronic studies in individuals with anxiety disorders and psychosis are sorely needed. Pharmaceutical companies are currently screening allosteric modulators of CB_1 and CB_2 receptors to find novel molecules that replicate desirable medical effects of cannabis without getting patients high. In the long term, they hope their novel

chemicals will supplant botanical cannabis in the medical marketplace.

Next, as promised, let's take a peek at CBD's bad and ugly sides. Earlier in this chapter, we alluded to the competition between cannabis retailers and the pharmaceutical industry. And just as Big Pharma undergoes periodic knuckle rapping and sometimes hefty fines from the FDA for aggressive expansion of drug sales into unapproved indications, the commodification of cannabis tends to encourage use of the plant and its derivatives outside areas where evidence suggests benefits. This is particularly the case for CBD products, where overly hyped, unproven claims of benefits tend to flourish for a relatively benign substance with few adverse effects, in an atmosphere of generally lax regulation. CBD's cachet derives from the frisson of its "edgy" association with cannabis plus its reputation as a cure-all for people and their pets—one that is essentially devoid of side effects.

It's important not to lose sight of CBD's proven benefits in intractable forms of childhood epilepsy and the many other medical conditions for which there are strong suggestions that CBD may also be helpful. Beyond these focused effective or promising applications, however, CBD is touted much more broadly as a product that can treat multiple medical conditions and symptoms. In addition, it is marketed as a general lifestyle enhancer and health-promoting substance. As such, it is sold in multiple forms: tinctures, oils, sprays, lotions, gummies, and even CBD-impregnated sportswear. Among its many claimed benefits are amelioration of chronic pain, insomnia, low libido, arthritis, inflammatory bowel disease, anxiety, peripheral neuropathy, and psoriasis. "It's a new kind of snake oil in the sense that there are a lot of claims and not so much evidence," said Dustin Lee, a Johns Hopkins psychiatrist.[69] Because the FDA still classifies CBD as a drug (although no longer Schedule I), it is not allowed to be sold in foods, drinks, or dietary supplements. Despite this, many of us will have encountered establishments in multiple cities selling CBD-infused sodas, coffees, smoothies, and candies. Some of these foods provide putative therapeutic doses, others not so much. Remember that epilepsy and psychosis trials have used CBD doses approaching 1,000 milligrams per day or more. Amounts in many over-the-counter products are typically a hundred times less than that. One industry analysis predicts the market for CBD products in the United States will reach $15 billion by 2025.[79] This claim seems wildly overblown, but it may not be. Major players have jumped on the CBD bandwagon. Gwyneth Paltrow's company Goop sells a variety of CBD-infused health and beauty products. The unlikely duo of Snoop Dogg and Martha Stewart host an Emmy-nominated cooking show on VH1, *Martha and Snoop's Potluck Dinner Party*, which features the substance. As mentioned in *Forbes* magazine, Canopy Growth, the Canadian cannabis behemoth, appointed Stewart their official company advisor for a new line of CBD products for people and their pets, and markets official Martha Stewart–branded hemp-derived CBD products to the US market; the company also helps market Snoop Dogg's Leafs by Snoop–branded cannabis products.[80] Similarly, Chelsea Handler has also launched a line of cannabis products.[81] And Kim Kardashian,

ever eager to get in on the act, hosted a CBD-themed baby shower in April 2019.[82] Thanks to all this publicity, CBD oil and CBD-containing products are seen as "hip" and sales for them are skyrocketing. "Wellness with an edge" is how Eleanor Morgan describes CBD consumer health products in the *Guardian*.[83] These highly touted CBD-containing consumables have become all the rage, and their soaring sales suggest their reign is just beginning.

So behind all the buzz (or in the case of CBD, non-buzz), what's the actual evidence that CBD is beneficial beyond a fairly narrow range of evidence-supported indications? Not only are claims for CBD being beneficial to one's mind and body in myriad ways mostly anecdotal at this point, but as mentioned above the doses contained in most consumer CBD products are pitifully low compared to those used in clinical medicine. While it's faintly possible that such CBD mini-doses in hummus, sodas, coffee, lip balms, tinctures, and body lotions may be beneficial to health, there is certainly no convincing evidence to support such claims.

An additional problem in CBD world is lax quality control. Outside of Epidiolex, CBD is not federally regulated by the FDA. Routine testing of samples of commercially available CBD oil has revealed widely different concentrations of the substance, disparate levels of accompanying THC, as well as various unwelcome contaminants, few of which were reported accurately on content labels. Thus, some unwary consumers of "pure CBD oil" derived from drug cannabis plants, rather than non-THC-containing hemp, have tested as THC-positive on routine employment drug testing.[84] The UK Centre for Medicinal Cannabis blind tested 30 purportedly CBD-containing products that they purchased online or in retail stores. Almost half of the products had significant detectable THC, making them illegal. Fewer than 40% of the products had CBD levels within 10% of the advertised amount.[85] FDA-approved pharmaceutical CBD is subject to rigorous purity testing, but for other commercial CBD-containing products, it's pretty much the Wild West.

How CBD is broken down in the body and how its levels in the blood change over time are well established. Like THC, CBD is a highly fat-soluble compound metabolized by enzymes in the liver and gut. When given by mouth, only about 15% of the CBD swallowed is actually absorbed; most of it passes out of your body unchanged. Think about that the next time you pay $300 for 10 mL (2 teaspoons) of 40% CBD oil.

As noted, despite Internet marketing implying that CBD products are legal to purchase, they in fact are not when marketed as having health benefits, rather than as a supplement or food additive. Currently, state and federal enforcement is lax in part because of the recognition that CBD is not intoxicating and does not lead to dependence. In early 2023, however, the FDA announced its intent to put more bite into its policing of CBD-containing products whose manufacturers make unwarranted claims regarding health benefits; many of us are watching carefully to see how that plays out in practice.

How do we best summarize the complex CBD story? Cannabidiol has genuine

therapeutic promise and already-demonstrated efficacy in a small number of conditions and one group of syndromes in particular—hard-to-treat childhood seizure disorders—that has already garnered FDA approval. On the other hand, the many broader claims made for the substance being useful in a startlingly wide variety of medical and psychiatric conditions run way ahead of the evidence. Hopefully that situation will change over the next few years as properly designed clinical trials clarify for what medical conditions, under what circumstances, and at what doses the drug is helpful.

Is cannabis useful in treating other psychiatric disorders?

Whether cannabis use helps or hinders long-term symptoms in anxiety and mood disorders is hotly debated and complicated by the fact that there are nonstraightforward relationships between dose and subjective effects. George Mammen and colleagues at Toronto's Centre for Addiction and Mental Health carried out a systematic literature review that sifted through over 10,000 citations to yield 12 relevant studies. These latter had followed a total of almost 12,000 individuals who had been diagnosed with conditions including depression, panic disorder, bipolar disorder, and PTSD for variable lengths of time up to five years.[86] The bottom line was that across 11 of the 12 studies, cannabis use over the last six months was associated with the patients with these disorders having higher symptom levels over time, compared to a similar patient group that used little or no cannabis. In addition, 10 of the studies also suggested that cannabis use was associated with less symptom improvement resulting from prescribed treatments such as medication or psychotherapy. Since the cannabis use in the subjects was self-reported and the cannabis itself was neither tested nor standardized in any way, these results are hardly definitive. But they do not suggest that cannabis has beneficial effects in these conditions. They also are consistent with prior studies reporting that reducing cannabis use is associated with improved mood in young women with depression.[87] Similarly, a very large Danish study showed that cannabis use disorder was associated with an increased risk of various types of serious depression and bipolar disorder.[88] At the risk of repeating the same message, the only adequate way to clarify these treatment issues is to put together a properly controlled trial of cannabis compared to placebo. Sue Sisley of the Scottsdale Research Institute has done just that, using NIDA-supplied marijuana in a sample of US veterans suffering from PTSD. She completed the study recently and found that government-supplied flower cannabis was not effective in relieving PTSD symptoms.[89]

What's the evidence for utility of medical cannabis in other conditions?

It's beyond the scope of this book to provide an exhaustive review of the massive, if generally preliminary, literature concerning various conditions in which various cannabinoid compounds seem to show some degree of promise. The reader is

referred to two recent excellent comprehensive reviews.[20,90] As I remarked earlier, it's striking that the conditions for which medical marijuana or its constituents are most frequently prescribed (insomnia, anxiety, pain, inflammation, nausea, and epilepsy) are almost precisely those to be found in historical pharmacopeias from ancient Assyria to Victorian-era O'Shaughnessy. Even the use of medical marijuana to increase appetite (in recent years used to help address weight loss associated with HIV/AIDS) is hinted at in a 16th-century book. This first mention of the "munchies" derives from Garcia da Orta, a Spaniard working for the Portuguese Crown in 1563. He published the first European account of Indian hemp originating in Portugal's contemporary Indian colony of Goa. "Those of my servants who took it, unknown to me, said that it made them so as not to feel the work, to be very happy, and to have a craving for food." [91] It's worth noting that, as is common in plant-derived medicines, cannabis also contains cannabinoids with opposite appetite-diminishing effects, such as THCV.

A very brief summary of conclusions from the comprehensive reviews referred to at the beginning of this section is that, in addition to the medical illnesses we reviewed earlier, there is moderate or promising evidence for the efficacy of different forms of cannabis or its derivatives in several diagnoses. Conditions repeatedly implicated are chemotherapy-related nausea and vomiting, weight loss associated with HIV/AIDS, neuropathic and inflammatory pain associated with multiple disorders, particularly the painful spasticity and neuropathic pain associated with multiple sclerosis. Evidence for efficacy in Tourette's syndrome, Crohn's disease, and ulcerative colitis is less convincing but suggestive. In many other conditions, evidence is either more flimsy or encouraging but very preliminary, or confusing and contradictory. These include Parkinson's disease, PTSD, agitation in Alzheimer's disease, addictive states (including opioid addiction), anxiety, various cancers, and finally schizophrenia (where outside of CBD, the evidence is that THC worsens rather than helps the disorder). All these claims need investigating properly.

Botany versus pharmacy

Let's confront an important botanical and pharmaceutical conundrum. On the one hand, numerous medicines in common use today (such as digitalis for heart failure and morphine for pain) originated as herbal plant extracts. They began their role in medicine as crude plant preparations, such as the leaves from foxglove or ephedra ("ma huang" in China) or the resin from opium poppy. But in every such case, the ultimate path has always been from the plant to a specific biologically active molecule (in these cases digoxin, ephedrine, or morphine) that can be purified, measured, and prescribed in precise doses. Appreciating that traditional sequence from crude plant to pharmacological essence provides the background to a key conceptual battle in the cannabis-medicine arena between natural-plant purists and synthetic pharmacists.

From a pharmaceutical company's point of view, the problem with plants is

that they are messy entities that were not designed by pharmacologists. For every desirable compound they contain, a plant often synthesizes a related chemical with an effect opposite to the one scientists seek. This requires complex and perhaps expensive separation of the two molecules. In addition, many natural drugs are "dirty." They commonly have diverse physiological activities and bind to a variety of receptor targets. These floral substances evolved in nature to help the plant—for example, to avoid predators or parasites—not to treat your inflamed kidney or to get you high. Besides, natural products are hard to patent. So from a business standpoint, it's ultimately more straightforward and certainly more profitable to custom design a compound in the laboratory that may resemble in its function something originally found in the botanical world but that is more powerful weight for weight, has a more specific "clean" effect on the intended target, and manifests fewer undesirable side effects. Cannabinoid pharmacologists dream of compounds many times more powerful and precisely targeted than the purest cannabis-derived dabs or shatter. And none of them will get you high.

From one perspective, pharmaceutical products and cannabis are both commodities. And among other motivations, people who develop and sell these products wish to maximize sales and profits. Benefiting secondarily from those profits of course are federal and local government agencies who derive income in the form of taxes. And let's not forget the lawyers and regulators who also stand to profit. So there's a significant tension between the pharmaceutical and cannabis industries that has both a philosophical and a commercial basis.

Let's imagine a face-off between pharmaceutical-company executives and medical-marijuana-dispensary owners. The executives will likely begin by arguing that cannabis contains multiple ingredients—literally many hundreds of cannabinoids, flavonoids, and terpenes. All these vary in their relative proportions not only from chemical variety (chemovar) to chemovar but even within a particular chemovar from batch to batch—not to mention the significant variation from the top of an individual bud to its bottom, within a single plant. "In contrast," these executives would say, "if you go to your local drugstore to purchase Tylenol, you'll find it has a single active constituent, and one tablet always contains precisely the same number of milligrams of only that ingredient. Besides that," they would add, "no one has performed the proper large-scale, randomized, double-blind, placebo-controlled studies to show that your favorite medical cannabis chemovar is effective for your specific illness. Or even worse, in most cases, nobody has even shown convincingly that cannabis works for that condition at all. The federal government won't ever allow us to license a plant. We can't patent it. And cannabis has major undesirable side effects: it makes people intoxicated and alters their behavior. We prefer to avoid lawsuits from people who crash their cars or space out while operating heavy machinery. From our point of view," they would continue, "getting high is definitely a bug, not a feature. Given all that, it's only logical for us to invest millions of dollars to create single-molecule drugs that act on the cannabinoid system in precise, subtle, and predictable ways, either by improving on natural plant cannabinoids or by

tweaking the enzymes that synthesize or break down our own internal endocannabinoid molecules. We're designing precision nano-tweezers, while you guys in dispensary land are still trying to cultivate the equivalent of a botanical sledgehammer or shotgun."

"On the contrary!" dispensary owners would exclaim in protest. "Cannabis's multiple ingredients are a help, not a hindrance, because they synergize entourage effects that are medically useful in ways above and beyond the utility of individual plant constituents. You pharmacology fat cats rely on exactly the same thing when you make cocktails of antiviral agents to combat HIV. So you would have to concede that drug combinations can be very effective. In our botanical world, terpenes help cannabinoids to cross the blood-brain barrier and to get where they are needed therapeutically. CBD tames THC's tendency to provoke psychosis. And there are likely many other beneficial pairings and interactions among constituents of the cannabis plant yet to be discovered. Please don't blame us for the sparse number of large-scale clinical trials. Cannabis is illegal at the federal level, and almost all cannabinoids are federal Schedule I drugs, making it almost impossible to conduct clinical lab studies using plant strains typically consumed in the real world. And we suspect you guys from Big Pharma lobby covertly to preserve cannabis's Schedule I designation. You don't want this helpful plant to be legalized because it threatens your bottom line. Consequently, the best evidence we dispensary owners can bring to the table is necessarily limited to small studies and anecdotal reports. But what we retail in our outlets is always going to be far less expensive than anything you pharmaceutical-industry titans can create in your giant factories. Unlike you, we have no need to recoup the millions of dollars spent on drug development."

This conceptual struggle between plant purists and synthetic pharmacologists is both ongoing and unresolved. While budtenders and dispensary owners ply their trade, drug-company pharmacologists plow ahead exploring compounds that act at cannabinoid receptors and modify the action of the relevant enzymes (that is, MAGL, FAAH, DAGL, and NAPE-PLD), which we encountered in the neuroscience chapter. Pharma (as the industry likes to call itself) has also explored compounds that don't cross the blood-brain barrier and act only peripherally, without any behavioral effects. (Remember that to them, getting stoned is a no-no.) Separating medical benefits from psychotropic effects can be difficult, however. Pharmacologists have tried for years with opium-poppy-derived compounds and their synthetic analogues to create pain relief without addictive potential. But in the long journey from opium to morphine to heroin to oxycodone to fentanyl, better pain relief has always proceeded hand in hand with greater abuse liability and increased lethality. So far, progress with the pharmaceutical industry's endocannabinoid drug development has been mostly discouraging, but nevertheless the enterprise remains full of promise. Toward the end of this chapter, we take a brief tour through the drugs that the industry has discovered and why their journey to produce commercially successful drugs that act on the endocannabinoid system, at least so far, has been the conceptual equivalent of a

slow climb up a steep mountain while onlookers jeer and throw sharp stones—in short, an unexpectedly arduous expedition by an industry already fraught with uncertainty.

How psychopharmacologists and pharmaceutical companies are building new endocannabinoid-related drugs

First, take a deep breath and cast your mind back to everything you learned about the neuroscience of the endocannabinoid system in Chapter 4.

A psychopharmacologist friend of mine likes to say that all drugs are poisons, whose properties humans can harness to work for or against us. An extrapolation of that line of thinking is that once we discover how a drug works biologically, we can begin to design compounds that achieve a similar result but are faster acting, more powerful, safer, and come with fewer side effects. Alternatively, we can craft compounds with converse actions to the parent compound. For example, if THC gives us the munchies, a drug with opposite effects can theoretically be used as an appetite suppressant. Similarly, a CB_1 receptor antagonist drug could be used acutely to treat individuals who have overindulged in edibles and have become anxious or psychotic; the pharmaceutical would compete with THC and kick it off the receptor site through which it exerts its actions. The most obvious starting point is to create new compounds in the lab that act similarly to plant cannabinoids but do so in a more efficient and targeted manner. Thus, several pharmaceutical development and manufacturing companies are focused on synthesizing new cannabinoid drugs. These are designed either to improve natural compounds found in the cannabis plant or to constitute novel molecules intended to produce effects on the ECS that are beyond the capability of current compounds found in cannabis. For example, such an ideal "designer drug" might be highly selective, producing strong, specific effects at only a single receptor. It might act, say, only at CB_2 and not at any other GPCR site either inside or outside the ECS. Pharmaceutical-company executives want to reach this goal for several reasons. As mentioned earlier in this chapter, it's not possible to patent a plant for therapeutic purposes, so there's no money to be made by investing in an elite team of botanical growers to create a super-duper cannabis chemovar that might be particularly effective in pain control. Drug manufacturers are masters of marketing patented novel compounds that they can sell at relatively high prices, both to recoup the development costs and to make a profit. Thus, a plant containing hundreds of compounds is completely outside their business model. A more likely possibility is for corporations to design synthetic cannabinoids with properties distinctly different from those found in the plant. One example might be an allosteric-modulator compound that fine-tunes the receptor's response to its naturally occurring ligands such as anandamide. How might Big Pharma achieve that goal, you may wonder? One approach is to use computer modeling to design molecules that are most likely to fit selectively onto cannabinoid receptor sites. Thus, a typical sight at a pharmaceutical company is a bevy of drug designers

using an automated program that behaves as a souped-up three-dimensional version of Tetris to suss out which of a series of candidate drug molecules fits best into a particular molecular docking site on a cannabinoid receptor.

An alternative approach is to design a novel therapeutic that boosts (or inhibits) the function of the ECS enzymes that synthesize or break down endogenous cannabinoids in the body. FAAH inhibitors, for example, are already in advanced clinical trials for a number of therapeutic applications, such as treating THC overdoses and minimizing cannabis withdrawal symptoms in individuals with cannabis use disorder who are trying to quit. For a recent review of FAAH and MAGL lipase inhibitor drugs, see van Egmond's work from 2021.[92] If Mrs. Smith's curious and candy-loving 5-year-old eats an entire poorly concealed, inadequately labeled box of a couple dozen 10 mg THC gummy bears, and she rushes her bairn, who is hallucinating and delirious, to the local emergency room, having a compound on hand that would allow medical staff to reverse his distress in minutes rather than hours would be truly useful.

Let's examine the practical issues in synthesizing such novel, non-plant-derived compounds. Plenty of pharmaceutical agents bind tightly (with high affinity) to the receptor that chemists are interested in targeting. The majority, however, are promiscuous, in the sense that they also glom on to a variety of other GPCR sites, completely irrelevant to the effect the pharmaceutical boffins are trying to achieve. As a result, the drug may trigger a bunch of unwanted, potentially dangerous off-target side effects, or physiological consequences that are the direct opposite of the ones you are aiming for.

Implicitly then, as well as specificity, an important property for an ideal drug candidate is clear-cut target engagement. A pharmacologist may synthesize a wonderful molecule that binds highly selectively to brain-cell CB_1 receptors in a test tube but in real life is unable to cross the blood-brain barrier and consequently never reaches its target. Or, equally frustrating, the lead chemist on your project may synthesize a drug that crosses the blood-brain barrier like a champion, producing undesired cognitive or psychiatric side effects, when he or she was designing it to act only peripherally, for example exclusively in the liver. Another hurdle lies in the very different distributions and numbers of cannabinoid receptors across the mammalian kingdom. A candidate agent may perform superbly in a rat model of a particular disorder yet be an utter flop in subsequent clinical trials with real human patients. These sorts of stumbling blocks bedevil pharmaceutical development companies large and small. They contribute in part to the long, bumpy, expensive, and more often than not unsuccessful road to developing new pharmaceutical agents; they're also one contributor to the high sales price of new prescription drugs.

To inventive research pharmacologists, these challenges encourage out-of-the-box thinking. And a great motivator is the potential for a great deal of money to be made. The global cannabinoid-derived pharmaceutical market was valued at $884 million in 2021, with a forecast of steady growth. Some drug companies have already learned to tweak fundamental chemical properties of cannabinoids. As we

saw in Chapter 4, classic members of the cannabinoid family are highly fat loving (lipophilic). Interestingly, lipophilic cannabinoid compounds are more likely both to result in toxicity and to accumulate in fat tissues, leading them to hang around for longer than desirable. Obviously, these are generally undesirable features in a drug compound.[93] Given the fat-loving nature of cannabinoid compounds, administering them via inhalation (or suppositories) is a highly efficient means of punting them rapidly into body tissues. Oral administration with a pill or capsule is preferred by many patients as a convenience and by pharmaceutical companies for their straightforward and standardized manufacture, however.

But here we run into a practical problem. We are now familiar with orally administered THC-containing preparations spanning the range from Marinol (synthetic THC dissolved in oil) all the way to edibles such as pot brownies and bhang lassi. But absorption of lipophilic compounds through the digestive tract is slow and highly unpredictable, both among different patients and even within the same patient depending on what he or she ate recently. Drug effects may kick in anywhere from thirty minutes to four hours after eating the product. Pharmaceutical drug designers are sticklers for predictability and hate that element of uncertainty (as doubtless do patients). They also want to avoid the potential for side effects and toxicity that goes along with lipid-loving drugs. So, wouldn't it be nice if the designers could use their ingenuity to craft a highly specific, fabulously selective ECS drug with high affinity and terrific target engagement that was more water soluble (and thus less fat soluble) than classic cannabinoids? This is not some pie- (or brownie-) in-the-sky idea. Starting with THC, molecular pharmacologists have already tinkered around to produce compounds that are much more water soluble than typical cannabinoids and are therefore more attractive, clinically feasible drug candidates.

CB_1 receptors are one of the most abundant GPCRs in the CNS and an obvious therapeutic target to exploit as neuromodulators in the treatment of neuropsychiatric conditions of many types. On the other hand, CB_2 receptors also have a huge amount of potential to be harnessed to treat targets for a host of diseases. Based on what we already understand about their function, pharmacologists could exploit their activity to modulate the immune system, dampen inflammatory reactions, tame pain, grow bone, and perhaps shrink cancerous tumors.

Because CB_2 receptors are also located in the central nervous system (although in drastically fewer numbers than CB_1 receptors) and mediate antianxiety responses, CB_2 receptor drugs might also have a role in treating certain psychiatric illnesses, such as anxiety and schizophrenia. Because CB2 receptors are diffusely distributed in the body and their function is less well understood than that of their CB_1 receptor brethren, until recently progress on this topic was still at the stage of baby steps and mere hopes.

Recently, however, scientists have made impressive progress working with CB_2 drug candidates.[94] Molecules are under development that are designed to tweak the immune system, reduce inflammation, and throttle back pain. A handful of

CB_2- active, selective agonist drugs with high affinity have been developed that show promise in humans. Two examples are cannabinor and tedalinab. In a complex and widespread system such as the ECS, progress is potentially booby-trapped with unexpected drug effects on multiple off-target systems. Let's review a few unfortunate examples.

One of the first such prescription compounds to reach the market was rimonabant, a CB_1 inverse agonist drug from the pharmaceutical company Sanofi-Aventis. Marketed under the trade names of Acomplia and Zimulti, the drug was approved for human use in Europe in 2006. The idea was that the medication would have the opposite effect at the CB_1 receptor from agonists or partial agonists such as THC and thus provoke the "anti-munchies." This in turn would result in reduced appetite, weight loss, and improvement in the so-called metabolic syndrome of combined obesity, hypertension, type 2 diabetes and high blood cholesterol. From that perspective, the drug was effective. In clinical trials compared to placebo, it led to significant, gradual weight loss. Unfortunately, rimonabant had to be withdrawn from the market. In a small proportion of patients who took it, it produced severe side effects of anxiety, depression, and suicidal thoughts. The risk of notable psychiatric disorders in people taking the drug was about double that expected to occur in the general population.[95] Thus, for safety reasons, the drug was removed from the market worldwide in 2008 before it could be approved in the United States. The FDA reasonably decided that the risks outweighed the benefits. In retrospect, rimonabant's adverse side-effect profile is utterly predictable. For most people, THC provokes effects of increased appetite along with mild euphoria, calmness, sociability, sleepiness, improvement in nausea, and calming of the GI tract. It's no surprise that the most commonly reported side effects of rimonabant, along with decreased appetite, were low mood, anxiety, crankiness, insomnia, nausea or vomiting, and diarrhea.[95]

Another drug design tactic is to explore pharmaceuticals that modify the enzymes that synthesize or break down natural endogenous cannabinoids, such as FAAH (also known as "nature's own buzzkill"). For a useful review see Tripathi's 2020 research.[96] This approach can have unfortunate, unexpected results. At the beginning of 2016, a stage 1 clinical trial in France of a novel pharmaceutical compound designed to inhibit FAAH went disastrously off track. The drug, BIA 10–2474, was designed by a Portuguese pharmaceutical company to treat various brain-based disorders. When trial doses were given to humans for the first time in order to test the compound's safety, one of the healthy volunteers given the medication sank into a coma and was ultimately pronounced brain dead. Another five participants needed to be hospitalized, two of them with severe neurological damage, which fortunately reversed within a few days. Because of these severe adverse events, the drug trial was immediately stopped. It's currently thought that the drug's activity outside the ECS (what drug companies call "off-target effects") was most likely responsible for the damage, due to it inhibiting multiple fat-metabolizing enzymes essential for brain function.[96]

At the end of 2020, pharmaceutical giant Pfizer spent $6.7 billion to enter the

medical-cannabis industry, signing an agreement with Arena Pharmaceuticals to explore a promising cannabinoid-based bowel-disease treatment. Pfizer is currently examining the experimental FAAH inhibitor compound PF-04457845, one of a class of drugs expected to boost brain anandamide levels. The medication was designed to ameliorate symptoms of cannabis withdrawal in individuals with cannabis use disorder. If the compound works as planned, it will lessen the usual withdrawal symptoms of insomnia, irritability, anxiety, and gastrointestinal distress. Based on the results of a preliminary clinical trial run at Yale by Deepak Cyril D'Souza's group, this FAAH inhibitor drug seems to reduce those symptoms. It produces about 97% inhibition of the FAAH enzyme's activity for two weeks. It is not psychoactive or subjectively rewarding, and it produced no withdrawal, tolerance, or dependence.[95] So, stay tuned for more news on this particular pharmaceutical. Pharma companies are actively exploring ECS-based drugs to treat a wide range of disorders. One intriguing approach is their use of techniques such as molecular modeling and chemical graph mining to see whether drugs already available on the market might act as FAAH inhibitors. Interestingly, one such massive recent number-crunching study identified the drug montelukast (marketed as Singulair and used to treat allergies and prevent asthma attacks) as a likely FAAH inhibitor that could be used to treat chronic pain.[97]

Outside of chronic-pain control, some of the more prominent areas of investigation for new ECS-active drugs include slowing cardiovascular inflammation and addressing cardio-metabolic disorders.[87] Positive allosteric modulators of CB_1 receptors have been suggested as potentially effective in treating post-traumatic stress disorder. The hope is that ECS-active drugs will also be used for effective treatment of several psychiatric disorders, including schizophrenia, anxiety, and substance use disorders. High on the pharmaceutical industry's target list are also epilepsy, irritable bowel syndrome, and various cancers.

To reach these goals, a number of hurdles remain. These include designing a series of ECS-active compounds that do not reach the brain and successfully avoid off-target effects (a particularly difficult demand in such a widespread signaling system). Achieving this necessitates acquiring a more thorough understanding of how plant cannabinoids exert their effects inside the body. At least for now, medical-cannabis dispensaries seem to be holding their own against the encroachment of pharmaceutical companies on their turf.

What happens next?

No US insurance companies currently cover medical cannabis, except for limited numbers of synthetic cannabinoids and plant derivatives listed earlier. The handful of currently available FDA-approved medicines are in general expensive and covered by some insurance companies only for their listed FDA indications, usually on a case-by-case basis. This situation needs to change. That will likely happen only when the FDA approves more cannabis products for medical use. In

turn, this will occur whenever federal and state governments both encourage and fund medical-cannabis research conducted under FDA clinical-trials standards. The FDA will hopefully standardize analysis and formulation of medical cannabis through regulation and licensing of drug production and distribution. We would benefit from better elucidating the physiological mechanisms underlying potential beneficial effects of cannabis and its constituents in particular medical conditions.[98] Better-quality standardized clinical trials may be able to demonstrate that there are indeed specific physiologic pathways or mechanisms through which cannabinoids are acting (for example, through endocannabinoid-related mechanisms related to specific disorders) rather than merely providing nonspecific subjective relief. Another problem: in the United States there are no prescribed medicines administered through smoking. We need to improve drug delivery systems for cannabis to include methods other than through the gut (the absorption of dronabinol is notoriously variable) or lungs (which are potentially irritated even by vaping). Improved sublingual and nasal sprays or tinctures seem to be an obvious alternative to explore. Drug companies are tinkering with self-emulsifying drug delivery systems and micro-encapsulation of cannabis constituents to help make absorption from the gut faster and more predictable.

This brings us to the insufficiently discussed issue of harm minimization. In general, harm reduction consists of a passel of policies designed to help reduce the unwanted social or physical consequences of particular behaviors. Providing sterile hypodermic needles to individuals with IV opioid addiction is one well-known example. Minimizing the harm from medical cannabis and its analogues is an essential issue to study in more depth, from the point of view of administering the drug safely as well as attempting to reduce predictable cannabis side effects and complications. For example: as has occurred with certain medications such as amphetamines, individuals recommending or seeking THC-containing medical-cannabis products may need to be made aware of preexisting conditions that raise the risks from using the drug. For example, those suffering from substance dependence, schizophrenia, or bipolar disorder may derive more harms than benefits from THC-containing substances. Currently, prescription-monitoring databases exist for drugs such as opioids to ensure that doctors are not overprescribing them in “pill mills” and that patients are not obtaining similar potentially abusable medicines from multiple physicians. There have been suggestions that similar provisions should be made for medical marijuana in an attempt to reduce potential harm to patients and to minimize the potential for diversion of the drug to the illicit market.

Ultimately, as has happened with many plant-derived medicines, it’s more than likely that in the long term, new powerful and specific synthetic compounds that target the endocannabinoid system will replace those found in the cannabis plant. Since such compounds can be patented by pharmaceutical companies, which can produce huge quantities of potentially profitable cannabinoids and other ECS-active compounds either chemically or by synthesis using yeasts or bacteria, this is an area of active investigation by such manufacturers despite initial stumbles.

Chapter 10

ECONOMICS

Marijuana: a $75 billion market by 2030?
SEAN WILLIAMS, Motley Fool, 2018[1]

Legalization should be limited to nonprofit production.
JONATHAN CAULKINS, "Against a Weed Industry," 2018 [2]

This chapter poses many interrelated questions. Who stands to benefit from sales following marijuana legalization? Large-scale growers? Dispensary-chain owners? Tobacco and vaporizer companies? Nonalcoholic-beverage retailers? How are they already getting into the game? Who loses? Do drug dealers, cartels, owners of prison businesses, possibly liquor distillers, and retailers all risk being disadvantaged? Should national or local governments be in the business of selling? Beyond these questions, we will also take a brief trip into another aspect of cannabis capitalism: accoutrements for the well-off cannabis consumer, including high-end bongs, vaping systems, glassware, and electronics. One strong thread in this chapter will be serious concerns regarding teenage use of cannabis and efforts to encourage their consumption.

Beneath the ongoing debates regarding marijuana legalization, the real story revolves around cannabis commercialization. They call it the "dot.bong boom." At least according to Havocscope's global black-market information website, marijuana occupies fourth place in the list of the world's biggest illicit businesses, at almost $142 billion, outranked only by counterfeit drugs, prostitution, and knockoff electronics.[3] From a financial perspective then, federal marijuana legalization in the United States is a big deal. How big is the United States' cannabis market? Cannabis is a consumer product transitioning to a trendy purchase that's moved from the counterculture to the culture counter. Free-market capitalism has cannabis as a commodity firmly in its sights. For North America as a whole, legal sales in 2017 jumped by one-third to almost $10 billion, with further annualized growth of nearly 30% through 2021, on track to reach nearly $25 billion by then.[4] In Massachusetts, for example, as of the end of 2023, adult-use retailers had seen more than $5.54 billion in total sales since opening in late 2018. Recreational sales also now make up the vast majority of legal marijuana sales in the state. Of the total for 2023, more than 87% ($1.57 billion) came from adult-use sales.[5] Bullish investors, looking forward to the year 2030, predict a $75 billion market in North America.[1] Many others, however, believe that estimates

like this are bloated and overly optimistic, blithely ignoring risks of oversupply and a likely significant fall in price per gram, as well as assuming that current patterns of consumption (for example, flower versus edibles) will remain stable. According to a recent article in *Forbes* magazine, the US marijuana industry in May 2017 was expanding so quickly that were it legalized, it would have total sales close to $45–$50 billion annually, greater than that of ice cream or movie tickets and ironically an order of magnitude greater than US sales of snack items beloved by stoners such as Doritos and Cheetos.[6] In 2016 legal cannabis sales alone in the United States totaled $4–$4.5 billion, still catching up on those for ice cream at $5.1 billion. Logically, Ben & Jerry's once proposed coming out with cannabis-infused ice cream, which would appear to be the ultimate self-selling product.[7] At our weekly laboratory meeting, suggested candidate flavor names included banana spliff, chunky junkie, cow-a-bonga, case the joint, and toasted bud. In addition to over-the-counter sales, legal cannabis brings jobs. A report in Marijuana Business Daily estimated that the cannabis sector employs between 165,000 and 230,000 full- and part-time workers, outnumbering bakers, massage therapists, and dental hygienists.[8] One knock-on economic effect is to boost real-estate prices, as cannabis businesses move into formerly vacant properties, attract tourism, and expand the local economy.

Where are things headed?

So, many businesses and would-be entrepreneurs, seeing the chance to make a profit from cannabis legalization, want in on the act. Investors started off bullish. Peter Bourne, Jimmy Carter's drug czar, stated in an interview in 2000 that as far back as the late 1970s, tobacco companies were exploring the market in the event that marijuana was legalized.[9] These large-scale commercial ventures will likely compete with small, local gourmet blends and so-called micro-potteries, paralleling the phenomenon of craft beers going head to head with the commercial brewing industry. The major concern here is that commercialization will greatly increase cannabis use, as has happened with tobacco and alcohol. We will return to these issues a little later in this chapter.

But more recently, in 2022, all this boundless financial optimism collided with economic reality. At least in Canada, post-legalization in 2018, too many dollars were chasing too few opportunities. The size of the cannabis consumer market was overestimated; burdensome taxes made legal retail prices uncompetitive, which helped a persistent black market; business competition cut into profits; and legal growers were left holding large stocks of unsellable weed.[10] A similar trend is affecting California. In part because cannabis is illegal at a federal level, difficulties in securing loans, transporting cash, banking legislation, and writing off business expenses, in addition to regulatory green tape, have all hobbled marijuana business ventures. "We are being overtaxed and overregulated," complained one retailer.[11] Canopy Growth, the Canadian pot behemoth, has burned through cash and as of April 2023 was a mere 34 cents away from

NASDAQ de-listing, with its stock price falling over 40% year to date.[12] This situation is emblematic of the Canadian cannabis industry.

Who may benefit financially from marijuana legalization, and who may potentially lose out?

State entities are a major driver of legalization because they hope the tax revenue generated from legal marijuana sales will bail out their state budget deficits. New York State, for example, estimated it would garner somewhere between $248 million and $678 million annually, depending on where it set the retail price of cannabis and the retail tax rate. The state correctly noted that these estimates were very preliminary, based on uncertainties regarding pricing, consumption, effects of legalization on the unregulated market, and whether prices would push consumers in the direction of the legal or illegal marketplace. In a report looking at the issue, a state commission observed that "some states overestimated revenue initially, as they did not account for the length of time it takes for a recreational market to become established, leading to fewer than expected sales." [13] Regardless, tobacco and soft-drink companies are pushing ahead with plans to invest in the cannabis industry.

One potential loser in a legal-cannabis marketplace is the US alcohol industry. According to the International Wines and Spirits Record, a British-based research group that analyzes the alcohol-beverage market, "Consumers will continue to look to cannabis products over alcohol for occasions when they are feeling creative, need to get motivated, or seeking health, medical or wellness benefits." Their report also notes that "not every dollar spent on legal cannabis is a dollar taken from alcohol—it is much more complex than that . . . but that there is a risk to alcohol due to legal cannabis, and the risk will be bigger as cannabis acceptance and consumption grows." [14] Similarly, the Molson Coors 2018 annual shareholder report worried that "the emergence of legal cannabis in certain US states and Canada may result in a shift of discretionary income away from our products or change in consumer preferences away from beer." [15] Daniel Rees, an economics professor at the University of Colorado, Denver, forecasted confidently in 2016 that consumers would substitute marijuana for alcohol. But an examination of that state's tax revenue suggests that following legalization, alcohol purchases have remained pretty rock steady.[16]

Naturally, alcohol companies are taking preemptive action by embracing the cannabis sector. They would far rather be potential winners than losers. For example, in 2018 Constellation Brands, owner of Corona beer and Robert Mondavi wine, invested $4 billion in Canopy Growth, the $10 billion publicly traded Canadian cannabis producer, as announced in the *New York Times* under the irresistible headline, "This Bud's for You." [17] Heineken has already begun marketing nonalcoholic, THC-containing sparkling water under the Lagunitas brand. And Aphria, the Canadian marijuana grow complex, recently recruited their new chief operating officer from Diageo Canada, the UK-based liquor

conglomerate that produces Guinness beer and several Seagram's products. The top 12 Canadian cannabis companies are worth around $42 billion and are reportedly pulling in investors hand over fist. One of the better known of these outfits is Tilray, based in British Columbia.[18] According to the *Economist*, "The industry is not particularly lucrative yet";[19] the 100 cannabis-related firms followed by Bloomberg lost $1.2 billion in 2021 (although some did make profits). Their overall revenues were a paltry $2.5 billion from a combined market value of $76 billion. The US Securities and Exchange Commission in 2018 warned investors about potential "investment fraud and market manipulation" with listed cannabis firms.[19] So, while eager investors sniff around for the coming "green rush," profits are still relatively elusive. In the meantime, Diageo, Coca-Cola, and Altria (the former tobacco behemoth Philip Morris) were apparently expressing interest in potential deals with Canadian cannabis companies.[19] These investment shifts from big tobacco and big alcohol to cannabis are occurring on a global scale. Imperial Brands, marketer of Kool and Winston cigarettes and the world's fourth biggest cigarette producer, invested a rumored $10 million in a British cannabis-research startup. Interestingly Snoop Dogg's investment firm also bought into the same enterprise, Oxford Cannabinoid Technologies. Imperial Brands had previously evinced interest by bringing on board a medical-cannabis-company chairman.[20] At the same time, alcohol companies are hedging their bets. The Intercept unearthed a campaign-financing report indicating that the Beer Distributors PAC donated $25,000 to various antimarijuana legislation initiatives in Massachusetts.[16,21]

Another set of potential losers in the world of legal pot is the class of individuals who have been sucked into the legal system for possession of small amounts of marijuana. In the future, such people will no longer garner criminal records or suffer from family disruption, job loss, or deprivation of voting rights. But there is a strong movement to push for people who've already suffered one or more of these losses to gain some sort of restitution or restorative justice in the form of employment in the expanding cannabis industry. Because of their past involvement with the substance, there is a certain argument for such people to be given a form of employment priority in expanding cannabis ventures. But currently, because of systemic bias against their race or ethnicity and low socioeconomic status, it is precisely these individuals and their communities who are most likely to be left behind. To tackle these problems, Massachusetts, for example, recently passed a law to train those jailed in the past for nonviolent marijuana offenses for jobs in the now-legal cannabis industry, and to help them qualify for assistance in raising capital.[22] Several cities in California have also started similar so-called equity programs.

Another potential loser is the illicit cannabis market, extending from low-level growers and street dealers all the way up the pyramid to drug barons and cartels. If cannabis is legalized, then the black market will shrink, at least in theory. That is true only to the extent that marijuana is not overtaxed in a way that encourages illicit purchases, for example, as happens with cigarettes in high-tobacco-tax states

such as New York. In Colorado and California, two early legalization states, significant numbers of users continue to purchase from their street dealers. This is because these dealers are individuals with whom buyers have built up trusting, quasi-social relationships over the years. And prices are cheaper on the illicit market, without all the expensive overhead. New York State's July 2018 assessment of marijuana regulation and legalization emphasized the possibility of "a reduction in violent crime due to the substantial reduction in the unregulated market, which would lead to a decline in home invasions associated with marijuana and the associated violence." [13]

A fourth obvious loser is the so-called prison industrial complex. Tens of thousands of individuals have been arrested for low-level marijuana-possession offences—arrests which disproportionately affect poor minorities and people of color. Enforcing these laws costs taxpayers money, and individuals who are locked up often get fed into for-profit private prison companies contracted by government penal agencies. These private companies profit from multiple aspects of incarceration, including construction, food supply, provision of medical care to inmates, hiring prison guards, and even providing probation services once inmates are released. Inmates themselves may constitute a cheap source of exploitable labor. Business models dictate that to maintain profitability, prisons need around a thousand beds, running at least a 90% occupancy rate.[23] Because of their nature, these profit-driven enterprises have an interest in maintaining or increasing incarceration rates. These companies have been often accused of lobbying legislators to pass stringent laws and judges to hand down longer sentences in order to accomplish this goal. More than any other factor, the so-called War on Drugs over the past 40-plus years has contributed to the expansion of the prison industrial complex. Those convicted for drug offenses, including cannabis transgressions, form a majority of the inmate population in US federal prisons.[24] A majority of those inmates are Black or Latino; in Massachusetts in 2013, 75% of inmates in prison for mandatory drug sentences fit that description, but a mere 22% of the state's population did so.[22]

What is likely to happen to cannabis prices over time?

Because of economies of scale related to industrial-scale production, costs to the consumer for legal cannabis will likely come down. As more large-scale producers get in on the act, cannabis will be cheaper to grow, process, and distribute. This trend already occurred in Washington State, where after-tax cannabis prices fell by 70% between August 2014 and August 2017.[2] Meanwhile, in Ontario, Canada, FSD Pharma has taken over an extensive former Kraft plant, with the aim of building the world's largest hydroponic indoor cannabis production and processing facility. By the year 2025, the company aims to produce 400,000 kg of dried cannabis annually and turn it into cannabis products. In 2019, it acquired a US-based research-and-development pharmaceutical company that will focus on developing synthetic compounds for therapeutic use that influence the

endocannabinoid system.[2] Jonathan Caulkins and his coauthors examine the pricing question in detail in their comprehensive book *Marijuana Legalization*.[25] The forces at play here are oversupply, leading to gluts, and state taxes, which if too high push consumers back to the illicit market.

Is youth marketing of cannabis in our future?

We've seen that the alcohol and tobacco industries have an avid interest in moving into cannabis sales. If there's one thing in which both tobacco and alcohol companies excel, it's targeting young people. The story of youth cigarette marketing through such cartoon characters as Joe Camel is well known. Perhaps less recognized is the alcohol-beverage industry's targeting of youngsters. The alcohol industry spends more than $2 billion annually promoting their products. Research carried out by the Center on Alcohol Marketing and Youth, at Johns Hopkins Bloomberg School of Public Health, found that magazines with substantial youth readership tended to feature ads encouraging alcohol overconsumption. Almost 25% of these ads contained sexual connotations or sexual objectification.[26] Youth are targeted by alcohol ads aimed at their age demographic. As multiple studies have determined, the more young people are exposed to alcohol advertising and marketing, the more likely they are to drink. Youth exposure to alcohol advertising is also associated with starting underage drinking, drinking more alcohol, and adverse health and social problems. Between 2017 and 2018, adolescents under the legal drinking age were exposed 28.5 billion times to alcohol ads on cable TV.[27] Sweet, fizzy alcoholic beverages such as alcopops are generally based on a malt-beverage, fruit-juice mixture. They are often sold in relatively inexpensive, large, brightly colored cans. Consuming one supersized alcopop meets the criterion for binge drinking in terms of the alcohol content. Although originally designed to attract millennials who disdain traditional alcohol tastes, popular brands such as Twisted Tea, Sparks, Seagram's Escapes, and Strawberry Rum Job are youth magnets. If and when recreational cannabis is legalized, one likely possibility is that all these advertising trends are immediately applied to this new commodity.

Given the above, what might happen in the worst of all possible worlds? Teens, at least in trendsetting Colorado, are already moving toward greater use of vaporizing, edibles, and dabbing.[28] If you were to ask me about my biggest concern regarding cannabis sales in the future, it's this scenario: Recreational cannabis is legalized at a federal level. Soon thereafter, high-THC, low-CBD extracts with attractive flavorings aimed at teens are marketed for use in pocket-sized, inconspicuous e-cigarettes, ostensibly to adult consumers. These products then rapidly disseminate into an enormous teenage marketplace. And finally, teen cannabis use multiplies quickly, with short- and long-term adverse health consequences. But before leaping headlong into alarmism over this issue, let's take a brief but instructive diversion into seeing what has played out in the world of e-cigarettes, officially known as "electronic nicotine delivery systems" (ENDS),

since 2006 when these vaping devices were first imported into the United States.

Alongside the battery and heating element, e-cigarettes contain a replaceable pod of liquids (e-liquids) that are a mixture of nicotine, flavorings, and moisture-preserving chemicals such as vegetable glycerin. Although these devices may help some adult tobacco-cigarette smokers cut their consumption or quit smoking, for youth and young-adult users, ENDS encourage both nicotine dependence and transitioning to regular combustible tobacco cigarettes. When the latter happens, prior e-cigarette use is associated with greater frequency and intensity of subsequent cigarette smoking, according to the National Academies of Sciences, Engineering, and Medicine 2018 report on the public-health consequences of e-cigarettes.[29] What's indisputable is that the number of teens vaping nicotine skyrocketed, and e-cigarettes became wildly popular among young people. Juul, resembling a flash drive, is the most well-known brand. Because it is relatively cheap, inconspicuous, and effective, it is way out in front in terms of brand popularity among ENDS, enjoying a 70% plus market share. Juul use increased nearly 80% in one year among high-school students and nearly 50% among middle-school students, with 3.6 million youths reporting that they used e-cigarettes in 2018, according to the 2018 National Youth Tobacco Survey. Although in that year, the US FDA banned sales in gas stations and retail stores of most flavored e-cigarette cartridges, they are still available for online purchase. There are plans to raise the minimum age for buying these and other tobacco products to 21 years.[30] The FDA has warned device manufacturers to stop marketing to teens or be banned. In fact, the FDA banned Juul products from being sold in the US in June 2022 because of toxicology problems but then granted the company an emergency stay. The FDA began a second reading review of Juul's data. "Tobacco companies have fought cutting flavors from e-cigarettes, saying they are not aimed at youths but at adults who need them as a way to transition from tobacco cigarettes. But health advocates point to the packaging and youth appeal of a variety of flavors, including chicken and waffles, rocket Popsicle and unicorn milk as well as fruity tastes like mango creme." [31] In the world of nicotine, e-cigarettes are seen as "different" from traditional tobacco cigarettes. Users are less likely to equate inhaling nicotine from a personal vaporizer with smoking or with the equivalent amount of the substance from cigarettes. Smoking a pack a day is an intuitive measurement; inhaling from a device is harder to quantify and keep track of. Major tobacco companies view e-cigarettes "as critical to their survival now that smoking rates have declined to their lowest levels in the United States." [32] In 2019 Altria, the US's biggest tobacco company with a $100 billion market value, and the maker of Marlboro, purchased a "35% stake in Juul, whose valuation soared on the investment to $38 billion." [32] Altria spent over $10 million on lobbying in 2018, while Juul spent $1.6 million. Despite that, the popularity of e-cigarettes, including Juul, has actually dwindled over the last several years, with sales falling by about 30% over the last few years.[32]

Moving forward, cannabis will likely be available for consumption in more forms that are cheaper and more convenient to use. Cannabinoid-containing oils

for use in personal vaporizers are likely to become extremely popular, copying nicotine e-cigarettes. Such products are already available at dispensaries in many states that have legalized marijuana. Since they are highly effective as a means of delivering cannabinoids, easy to conceal, and convenient to carry around, they are likely to be increasingly adopted. It's the logical next step that I believe should definitely be avoided, as mentioned a little earlier. If the pods for "e-joints" also contain teen-attracting flavors such as mango creme, even if officially marketed to adult users, they will predictably become immensely popular among teenagers. If the price is kept low, this will be a super-desirable product for teens. Other related, possible nasty combinations to be equally shunned would include "e-spliffs" containing super-addictive nicotine-THC combinations and teen-targeted "e-joint" marketing campaigns featuring cartoon characters. Joe Camel, meet Marley the addictive and harm-maximizing Rastafarian magpie. But in 2019, outbreaks of serious lung illnesses (EVALI) and deaths likely related to vitamin E acetate in vaping products (especially as an additive in THC-containing e-cigarettes) threatened the burgeoning vaping and e-cigarette market. In response to the illnesses and deaths, many states banned vaping products containing vitamin E acetate.[33] In 2023, the CDC reported the prevalence of EVALI had substantially reduced, probably owing to many reasons, including rapid public health action to increase public awareness.[34] This story is one that continues to evolve.

Smart Approaches to Marijuana (SAM)

In the context of all the earlier-mentioned developments, Smart Approaches to Marijuana (SAM) is worth a mention.[35] This lobbying organization was cofounded in 2013 by former congressman Patrick Kennedy (D-Rhode Island) and Kevin Sabet. Kennedy, the youngest son of the late Senator Teddy Kennedy, has been frank regarding both his prior abuse of and addiction to various substances (cocaine, alcohol, prescription opioids) and his diagnosis of bipolar disorder. He has been a consistent supporter of federal legislation designed to improve addiction and mental healthcare delivery and helped found the One Mind research initiative to promote neuroscience discovery impacting mental-health issues.[36] (Patrick is a different person from his cousin Robert F. Kennedy Jr., the environmental-law specialist. RFK Jr. is also a health activist, but he has spread misinformation about childhood vaccines and their association with autism, through the organization Children's Health Defense, which he chairs, as well as about supposed conspiracy-linked dangers of COVID-19 vaccinations. As of this writing in 2024, RFK Jr. is running as an Independent presidential contender.)

Patrick Kennedy's SAM cofounder, Kevin Sabet, is a long-standing antidrug crusader with a particular focus on marijuana. Sabet is a former three-time advisor to the White House Office of National Drug Control Policy and, like me, on Yale's faculty. When it comes to cannabis, he is effectively a prohibitionist. (See Joe Dolce's interview with Sabet in the former's book, *Brave New Weed*.)[37] SAM's abiding concern when it comes to cannabis legalization is that America is

in the process of creating a new Big Tobacco scenario. SAM now encompasses a multistate lobbying group with a fair amount of clout that inserts itself into many statewide cannabis-legalization initiatives. The group is well funded and uses effectively organized public-information campaigns that bring in national figures to testify before legislatures in any state considering legalizing recreational marijuana. Given the complex interrelationships between corporate lobbyists, politicians, political action committees, and one-off state initiatives, it's important to know where SAM's funding derives from, although this information is hard to ferret out.[37]

SAM generally supports cannabis decriminalization, but not legalization, and is concerned (some would say overly concerned) about public-health repercussions of marijuana legalization. It generally encourages both medical-marijuana research and the development of FDA-approved cannabis-based medicines. One of SAM's main aims is to counter the "predatory" pot industry,[38] which as we've learned is indeed becoming increasingly entangled with Big Tobacco and Big Alcohol. I share SAM's concern on this major topic. Clear lessons have emerged from the marketing strategies of alcohol and tobacco conglomerates. Commercial marketers for profitable consumable products such as cigarettes and booze push hard to set prices low in order to boost sales, and they rely on continued consumption by the minority of frequent (daily) users who purchase the overwhelming majority of the product. Or as Mark A. R. Kleiman phrases it, the cannabis "industry will do everything in its power to create and sustain the biggest possible population of chronic stoners." [39]

SAM ostensibly promotes the view that our national and international drug policies should be founded on science, a principle that chimes with the intent of this book. But the organization concludes, from their own examination of the available scientific evidence, that cannabis should remain illegal.[40] This is not my judgment. I find their overall position on marijuana logically untenable. Their policy reminds me of the old joke about your uncle the cop, who, after sharing a joint with you, promptly arrests you for drug use. Karen O'Keefe, director of Connecticut state policies for the Marijuana Policy Project, believes that SAM plays fast and loose with the facts. For example, she states that their testimony in June 2019 during a failed legislative initiative to legalize recreational marijuana in Connecticut was misleading on a couple of fronts, "including inaccurately claiming that marijuana use went up among teens in Colorado (after legalization in 2014), when it actually went down, and falsely claiming the graduation rates went down, when they went up." [41]

So let's take a look at SAM's policy positions. I would summarize these as antilegalization, partial decriminalization, opposition to harm-reduction policies, and skepticism toward initiatives to tax and regulate marijuana. A careful reading of SAM's policy and press statements, website, and numerous related publications, leads me to think that implementation of their main agenda would translate into only minimal change to the status quo. SAM states (I believe quite reasonably) that they oppose greatly enriching a small number of pro-cannabis

businesspeople. But they have little to say regarding the immense amounts of money already being poured into the War on Drugs by federal and local governments, including policing and incarceration expenses that are ultimately taxpayer financed. SAM also states that they are extremely concerned that cannabis legalization will lead to a rapid wave of high schoolers and teenagers becoming cannabis dependent.[40] But as we saw in Chapter 6, such rates have stayed steady in those states that legalize recreational cannabis. Outside of science-based issues, Sabet relies on cultural arguments. For example, he states that "alcohol, unlike illegal drugs, has a long history of widespread, accepted use in our society, dating back to before biblical times. Illegal drugs cannot claim such pervasive use by a large part of the planet's population over such a long period of time." [42,43] But that view is contrary to the historical facts I summarize elsewhere, which illustrate that societies in India and the Islamic worlds learned to accommodate successfully large-scale public consumption of cannabis in various forms. And as we have seen, cannabis was used in biblical times as a sacrament. Besides, Americans are ever eager to adopt a panoply of desirable foreign customs ranging from eating quinoa, sushi, and goji berries to driving compact vehicles.

It's all about marketing

Speaking of those gaining from legal cannabis sales, in the world of marijuana-themed product marketing, the Higher Standards store in New York City's Chelsea Market is an example of a non-dispensary purveyor of literally high-end accessories for well-heeled, stylish cannabis users. This establishment is several steps up from the usual head shop in terms of atmosphere, decor, and price. As Katherine Bernard stated in her *New York Times* article, "You can buy cannabis accessories in a room with exposed brick and industrial-inspired shelving, just like at a place where you can buy all of your other class signifiers. . . . If high is highbrow, then cannabis can be consumed tastefully and stylishly, like cupcakes or wine." [44] Elsewhere in the United States, skilled glassblowers have produced high-end cannabis-related objects embodying beauty and fine craftsmanship that can cost you $100,000 or more. Some examples of super-expensive bubblers, dab rigs, and bongs can be found in an article on Wikileaf's website.[45] Meanwhile, at the inexpensive and illicit end of the market, the US DEA in Oakland and Emeryville, California, succeeded in inducing several individuals to plead guilty for their role in manufacturing and distributing marijuana-infused products that mimicked familiar candy bars, in slightly disguised form, with names such as Puff-a Mint Patty, Twixed, Pot Tarts, and KeefKat. And legally, thanks to advances in nano-emulsification technology, cannabis-infused beverages are starting to become consumer favorites.[46]

What are some of the procedural hurdles to overcome?

How do we tax legalized cannabis? This is dynamic territory because any chosen strategy likely evokes a consumer countermove. If tax rates are set too high, then

this pushes consumers back to the illegal market. This has likely occurred in California, where almost three-quarters of cannabis purchased is still sold illicitly.[47] But if tax rates are set too low, then this encourages overuse with its concomitant risks. Although states that have legalized marijuana had originally hoped for significant revenue boosts, they generally failed to predict just how steeply prices would fall. One proposed strategy is to tax cannabis by weight.[48] California does this; Maine began this policy in 2018. The obvious consumer counterstrategy is to purchase concentrates and get more bang for their buck. Thus, states will need to either set a limit on THC potency (as does Connecticut) or figure out a complex formula to tax by the amount of THC being sold (again, as Connecticut decided to implement). For example, back in 2013, the Netherlands reclassified more-potent cannabis products (defined as having THC of 15% or more) under a legally restricted drug schedule. Taxing in this manner correlates better with level of intoxication, similar to the system used with alcohol. The consumer reaction to similar restrictions in the United States would likely encourage illicit production and sale of butane hash oil and similar concentrates. As a related issue, when all types of cannabis products are available for legal sale, how can taxation be somehow made both equivalent and fair across edibles, concentrates, flower, and tinctures? One possibility is to have a simple retail-price-based tax. States are wary of this approach because it is potentially a more unstable revenue source. States seeking income through taxation also worry about where to set the limits on cannabis plants grown by individuals, which by definition remain untaxed.

Banking and money laundering is another thorny issue. Under the 1986 Money Laundering Control Act (MLCA), banks are prohibited from providing financial services to any business engaged in illicit activities. Because at a federal level, marijuana is still illegal, cannabis sales even in individual states that have legalized it are by definition illicit under the Controlled Substances Act. In July 2019, the US Senate Committee on Banking, Housing, and Urban Affairs held a hearing to review a bill, the new version of which is called the Secure and Fair Enforcement Regulation (SAFER) Banking Act. The bill has repeatedly stalled and hasn't yet passed, but if enacted, this legislation would allow federally supervised financial institutions such as banks to have cannabis-related businesses as customers.[49] According to Ben Curren's article in *Forbes* magazine, the bill would protect banks from federal prosecution as long as the cannabis businesses they work with comply with the laws in the states where they operate. The act was proposed in order to "create protections for depository institutions that provide financial services to cannabis-related legitimate businesses, and service providers for such businesses." [50] The major purpose of this act is to increase public safety by ensuring access to financial services to cannabis-related legitimate businesses and service providers, and reducing the amount of cash at such businesses. According to the *Washington Post*, cannabis dispensaries have dropped off duffel bags and suitcases full of cash to pay their taxes, sometimes driving hundreds of miles to do so.[51] Currently, the cash-only nature of dispensary transactions makes

them potential robbery magnets. The worlds of legal cannabis retailing and those of blockchains and cryptocurrencies are thus fated currently to buddy up to one another. Another issue is the following. Because cannabis is currently a Schedule I drug, it falls under section 280E of the US tax code. Businesses that sell such substances are not allowed to take the normal corporate income-tax deductions, except for the cost of the goods. This results in extremely high tax rates for profitable businesses, as well as an inability to take standard business tax write-offs. Currently, all those dollars accrue to the federal government. And this revenue source would shrivel up were cannabis to be legalized federally. The government may be disinclined to lose this income stream unless it can find an alternative. How the current tax revenue would be offset by federal cannabis legalization leading to a larger market, and thus more sales at a lower federal tax rate, is not altogether clear.

What are some alternative possibilities?

Several cannabis-concerned economic thinkers have pushed out-of-the-box ideas when it comes to marijuana production and sales. Nonprofit production is one. This is not just a pipe dream of ageing hippies but has been mooted as a serious consideration by Jonathan Caulkins of the RAND Corporation.[2] He argues that the debates over cannabis legalization immediately narrow the focus to bypass numerous viable but usually unconsidered options contained within the legalization umbrella. These range along a wide spectrum from small-scale personal cultivation to large-scale commercial sales. Caulkins proposes several novel ideas that would gradually phase out for-profit businesses. These businesses could be replaced by nonprofit organizations whose boards would aim to protect public health and constrain demand to current levels. Optionally, cooperatives could supply only their own registered members. Another of his considerations revolves around the possibilities that might occur if we treated marijuana like alcohol.[25]

This chapter attempted to provide a 20,000-foot view of the tangled universe of commercial cannabis. Resolving these issues will be one essential part of the future of federally legalized cannabis. How this future may shape up is the theme of the next chapter.

Chapter 11

A SCIENTIFIC APPROACH TO CANNABIS LEGALIZATION

> Very few drugs, if any, have such a tangled history as a medicine. In fact, prejudice, superstition, emotionalism, and even ideology have managed to lead cannabis to ups and downs concerning both its therapeutic properties and its toxicologic and dependence-inducing effects.
>
> E. A. CARLINI, "The Good and the Bad Effects of (-) Trans-Delta-9-Tetrahydrocannabinol (Delta 9-THC) on Humans," 2004[1]

It should be clear from the prior chapters that federal legalization of recreational cannabis is likely (but not definitely) on the horizon in the United States. My guess is the odds are 50:50. Exactly what such a future will look like is speculative. But given the scientific information we have reviewed, some of the key problems that will follow legalization, as well as benefits, are predictable. Science raises important questions and suggests appropriate answers. Informed by available research, how can we best formulate plans and policies to minimize these potential harms and to make cannabis use as safe as possible? If education and drug treatment are included in these policies, who will pay for them? What is the future of medical marijuana? Where will our cannabis come from down the road? Will it be grown in greenhouses, hydroponic facilities, agricultural fields, or tanks of yeast? This chapter entertains some of these questions and ways to address them.

Cannabis is the most commonly used illicit drug in the world. As a recreational substance, it is particularly favored among adolescents. If you have read this far, you will understand that the drug offers unique subjective experiences to its users from a recreational point of view and that it may also have important medicinal properties. Like all drugs, however, it is associated with known undesirable side effects and harms. It has evolved from being a pariah substance to one that 70% of the US adult population thinks should be legalized.[2] Support for marijuana legalization currently matches that for same-sex marriage.[3] Talking with legislators, physicians, and businesspeople, the message I hear is the same. Federal legalization is a "runaway freight train," the "horse has already left the barn," it's "too late to turn back the clock," and "it's inevitable now."

So the United States is more than likely to embark on a significant social experiment akin to the repeal of alcohol prohibition. One consequence of legalization is inescapable. There will be more users—and that translates

inevitably to more problems. Simple statistics tell us that even if the percentage of individuals experiencing harm from cannabis is small, if their overall number is very large, then many people are affected. So, for the sake of argument, if 10% of cannabis users become dependent, then 10% of 120 million people (50% of the number of the US population over the age of 21) is a huge number, if each one of these individuals chose to get high regularly. Similarly, the more people who use cannabis, then the more cases of psychosis and more intoxicated driving incidents will occur. The problems though will occur most often not in the vast majority of moderate or occasional cannabis users but in the approximately 20% who will use frequently if not daily. This minority consumes large amounts of the drug and will tend to favor high-THC-containing forms of cannabis, because these products get you higher faster and cheaper. Jonathan Caulkins estimates that the 20% of users who consume cannabis products several times every day actually account for about 80% of the marijuana consumed.[4] Alcohol-beverage consumption follows a similar template. That pattern is one of numerous moderate users but with around 20% of really heavy drinkers who consume a similar significant proportion of alcohol sold. One little-asked question is what the quality of life is like for individuals who smoke cannabis every day on multiple occasions. Currently, there are over 8 million of these people. In a statistical profile, up to 31% of the adult habitual users are more likely to have a high-school education or less and to have some level of impairment in work, school, and relationships.[5] There is also an association of heavy daily use with lower income, unemployment, and decreased life satisfaction.[6,7]

In planning for this future, to paraphrase J. G. Ballard, what the legislators of today decide, society will live with tomorrow. Science, with its dependence on facts over emotional appeals, should help guide this process. But science-based reports can be easily buried, as was the fate of the LaGuardia Committee's advice in 1944 (condemned by Harry Anslinger, commissioner of the US Treasury Department's Federal Bureau of Narcotics) and the Shafer Commission's recommendations in 1972 (ignored by Richard Nixon). When the scientific conclusions are unacceptable to those in power, then the messenger is, if not literally shot, consigned to some form of limbo along with their report. Scientists need to plan ahead to avoid being similarly silenced.

According to Susan Weiss of the National Institute on Drug Abuse, scientific knowledge and discovery can influence public policy regarding cannabis in several important ways.[8] To get this advice across to decision-makers most effectively, she says, a few key considerations always need to be kept in mind:

- Public-health interests, not monetary ones, must be primary when making policy decisions.
- The scientific knowledge we have available right now needs to be better disseminated; there are too many myths and too much misinformation about cannabis that need countering by available facts.
- We need to build on our existing scientific knowledge base with further

research.

- Since marijuana legalization is such a polarized issue, scientists need to be clear with the public, both about what we know and equally what we don't know.
- The public also needs to hear what's understood about real-world questions regarding cannabis, such as addiction, teen exposure, and use during pregnancy—in other words, not a blanket "pot is bad" message.
- In speaking about cannabis, when dealing with issues such as limiting drug potency or prohibiting certain products, it's super-important to use the correct terminology—for example, distinguishing plant marijuana from synthetics such as K2 and from concentrates such as dabs.[8]

So, in speaking with decision-makers, what are some of the salient facts requiring emphasis? To reprise, cannabis is both a medication and an intoxicant, like a variety of such dual-purpose substances, which also includes opioids and cocaine. Cannabis though is associated with more moderate harms than those drugs when used recreationally, and it is gaining in popularity. According to a survey conducted in 2023, 17% of American adults smoke marijuana, and around half of adults in the United States declared they had tried marijuana at least once. Over the last decades, this percentage has seen an increase. Additionally, a majority of the US population now favors legalization.[2,9] We know that cannabis, although definitely a less harmful recreational substance than either tobacco or alcohol, is now stronger in terms of THC content than the drug familiar to baby boomers, and it thus carries more potential risk. The point of recreational-marijuana legalization, though, is not to replace alcohol or tobacco with cannabis but to introduce an additional intoxicant that requires judging on its own terms. In legalizing any new recreational substance, an essential consideration, which we will discuss in this chapter, is how to most effectively minimize the drug's associated harms. Many legislators are averse to discussing harm reduction, but such a conversation is essential. Substance legalization always represents the devil's bargain. Recall that the US elected (after a brief failed experiment with prohibition) to legalize beverage alcohol, a much more harmful drug than cannabis, as reviewed earlier. Legalization proved to be a popular choice. According to the 2016 National Survey on Drug Use and Health, 51% of those aged 12 and older drank alcohol in the prior 30 days.[10] We do not automatically call such moderate drinkers "alcoholics." As with alcohol, the vast majority of cannabis users indulge moderately and suffer no ill effects. Nevertheless, for cannabis there are several major concerns, and because of the ongoing opioid crisis, US policymakers want to avoid unleashing new drug-related problems. The first major concern is that, as has happened with alcohol, underage use will become very common, especially on college campuses. Diversion of cannabis from dispensaries to teenagers, with their vulnerable brains, is an especially concerning related issue that will prove challenging (but not impossible) to

prevent.

Marijuana is now available in multiple dosing forms, including the increasingly used edibles and vaporizing devices that were either virtually unknown or much less common in the United States even a decade ago. Although, as we've seen, edibles have been used in Indian festivals such as Holi for thousands of years. Irrespective of how it's administered, the drug has risks, and yet another concern is that of cannabis abuse and dependence. Around 10% of continuing users will develop dependence (although physical withdrawal is relatively milder than with many other recreational drugs). A major worry is the drug's association with risk for psychotic illnesses, including schizophrenia. Odds of developing such an illness rise with how often cannabis is used, how much THC it contains, and probably how young the user is when he or she begins consuming it. Finally, the drug impairs academic performance (as we saw in the college students of the BARCS and the Dutch research studies) and is associated with intoxicated driving-related accidents. Again though, likely to a lesser extent in each of these examples than with alcohol. To different degrees then, all of these concerns are justified, as detailed in prior chapters.

Before we dive into harm reduction in detail, I think it's useful to discuss some general issues regarding cannabis legalization. First, it's important to realize that impending federal legalization is not absolutely certain, despite the many indicators that suggest this is in the cards. Even with the growing number of state-licensed marijuana businesses in existence, and ever-increasing pro-legalization public sentiment, a restrictive federal government could, should it choose to do so, decide to enforce existing laws and close down every single dispensary nationwide. If legalization proceeds though, how might things (so to speak) roll out? Harking back to the last chapter, the most likely emerging model, although by no means the only one, is a repeat of the alcohol paradigm. Under this scenario, for-profit corporations produce cannabis, sell it on the open market, and heavily advertise its use. That's according to Jonathan Caulkins, a professor at Carnegie Mellon University and codirector of RAND's Drug Policy Research Center in Santa Monica, who has written clearly and intelligently on this issue.[11] An alternative model is legalizing cannabis analogously to tobacco. This implies focusing on short-term reduction of the product's use and its long-term extinction. Powerful commercial lobbying efforts as well as consumer sentiment make this scenario much less likely. Legalizing cannabis like alcohol focuses on harm reduction but not restricting sales, other than to vulnerable individuals such as teens. As Mark A. R. Kleiman termed it, this approach would be "weakly regulated commercialized legalization." [12] As we saw in the prior chapter, the negative side of this model is that Big Tobacco and Big Alcohol will try to sell as much product on a large scale as cheaply as possible and to market it to youth in order to build lifelong consumers. We've learned from the targeting of Juul fruit-flavored nicotine vaping products to teens, and from Joe Camel advertisements, how this particular scenario is likely to unfold.[13] So part of harm reduction is to anticipate such moves and to think about how to counter them.

To better anticipate the harms associated with widespread use, the federal government would be wise to change THC's Schedule I status and to allow more research on these problems. As one aspect of this, they will also need to give researchers access for their experiments to multiple sources of marijuana that more closely resemble what's available to consumers. This menu will include concentrates, edibles, tinctures, and flower marijuana from different sources that reflect the range of THC and CBD available in the real world. Recommendations to reschedule cannabis from the current Schedule I, defined by high potential for abuse and no medical use (other examples are heroin and LSD) are already in the works as of 2023. If enacted, cannabis would move down the scale to Schedule III, defined by accepted medical use with lower abuse potential (a typical example is Tylenol with codeine).

The relevant entity, likely the National Institute on Drug Abuse, will definitely need to source this material from more than a single relatively small-scale supplier at the University of Mississippi. This effort may be underway as the result of a recent physician-scientist-initiated lawsuit, but prolonged foot dragging is equally likely. Another aspect to recognize is that while we have been discussing cannabis use as an isolated phenomenon, it can of course occur alongside consumption of alcohol, tobacco, and other drugs. Because of the possible synergism between alcohol- and cannabis-related impairment, this mix-and-match consumption raises special concerns about, among other outcomes, driving while intoxicated and work-related accidents. Similar concerns arise for co-use with tobacco, where health concerns are important.

We've learned a lot from epidemiology in terms of what outcomes to expect from boosted cannabis consumption, and our neighbor to the north is already beginning to yield practical observations. But it will likely take decades to figure out legalization's longer-term consequences. Some policymakers are already grappling with these issues based on the experience of Colorado, California, and other states that have legalized recreational cannabis. In July 2018, New York State published a lengthy and fairly comprehensive document outlining their assessment of the potential impact, risks, and benefits of regulated marijuana for the region's health, criminal justice, public safety, economics, and education.[14] Some of their conclusions are provocative, although many could be classified as overly optimistic; for example, "changes in overall patterns of use are not likely to be significant. . . . There is no conclusive evidence about whether legalizing marijuana increases use. . . . Brief increases in use in Colorado and Washington leveled out . . . [but] a regulated marijuana program should monitor and document patients' abuse to evaluate the impact of legalization." [14] The New York subject-matter experts also doubted that legalizing cannabis would increase use among youth and noted that there would likely be a reduction in the use of synthetic cannabinoids. They recommended that an appropriate regulatory framework "could support a more appropriate level of treatment for marijuana use that focuses on harm reduction." [14]

What might sensible, science-guided harm-reduction strategies look like in the

US and elsewhere? Many possibilities exist to minimize harm and maximize benefits. Some of these are more practical to enforce and more desirable than others. Deepak Cyril D'Souza and his colleagues at Yale have devoted a fair amount of time to enumerating public-policy proposals that have influenced some of the initiatives I explore next.

Set age limits on cannabis sales

Teens are uniquely vulnerable to cannabis effects, from increased psychosis risk to (disputed) effects on IQ, associations with reduced academic grades, and (perhaps reversible) impaired educational and occupational attainment. Restricting sales to minors, with rigorous proof of identity and significant penalties to both purchasers and vendors for underage sales would all seem to be necessary and sensible policies. Indeed, these are the national measures pursued by Canada during its 2018 federal legalization process. One obvious question is what the minimum age for cannabis sales should be. Remembering Susan Weiss's admonition that scientific considerations should take priority over commercial ones,[8] and having learned about frontal-lobe development and neural-pruning trajectories in the human brain, we can make a few recommendations here. The lower age limit could be either 18 (as in most of Canada), 21 (as in Quebec), or possibly 25 (the notional endpoint of the neural-pruning process). If we are guided more by the estimated neurobiology of pruning and the psychosis risk data from the Dunedin study, the safest age would be 25. If we are led more by practicality, then 21 is the age where legal limits would most likely settle. In the real world, neurobiology is likely to compromise with feasibility to settle on age 21. Similar to buyers in Canada, dispensary customers would need to confirm their age with a rigorously checked federal or state official ID, and there would be severe penalties for underage purchases for both the buyer and the dispensary. Purchasing cannabis on behalf of an underage customer is also strongly sanctioned in Canada. Again, I believe these are sensible policies.

Limit drug potency

Numerous studies, most convincingly the recent Di Forti investigation,[15] demonstrate that cannabis potency is a major driver of psychosis-associated risk. So control of THC strength, for example by restricting the sale of concentrates and dabs, or perhaps mandating THC-to-CBD ratios, would seem to be indicated. Some US states such as Connecticut already ban the sale of concentrates to recreational-cannabis customers. Passing such legislation, however, might have unintended consequences, such as encouraging an illicit market in the banned high-potency substances. The resulting rash of home-brewing burn victims and butane-contaminated concentrates that would accompany uncontrolled homemade BHO manufacture with its untested product would have to be weighed into any decision. The Netherlands did ban THC concentrations that exceed a certain arbitrary limit, but such enforcement is more practicable in Holland than in the

United States.

An important related issue is how cannabis users have changed their drug-use behavior in response to the high-THC cannabis now available. The assumption of many anti-cannabis advocates is that high-THC chemovars necessarily have adverse effects because of their potency. But this line of reasoning isn't accurate when individuals accustomed to drinking low-alcohol "near beer" gain access to distilled spirits such as whiskey. Such people don't imbibe equivalent volumes of whiskey but generally modulate their alcohol intake to reach the same degree of intoxication. This question hasn't been intensely studied in the cannabis world, despite its relevance. Korf and colleagues, however, surveyed Dutch "coffee shop" cannabis users and found a tendency for them to adjust for stronger cannabis by smoking smaller amounts and inhaling less deeply.[16] Nevertheless, the Di Forti data are compelling in linking THC potency to psychosis risk. So concerns regarding THC percentages cannot simply be dismissed.

The bottom line is that limiting drug potency is a terrific idea in theory but hard to implement in practice and likely accompanied by negative outcomes. The unknown but crucial fact is whether the number of cannabis users protected from legal high-THC cannabis by legislation is outweighed by the size of the population who will be harmed by purchasing or home brewing illegal high-potency forms of the drug. There is no easy, a priori method to predict the relative percentages of each group.

Reduce cannabis consumption rates

Various strategies for curtailing sales have been proposed. Here's a possible way forward. We can limit the amount of product sold to one individual during a single sale and restrict the locations where cannabis products are sold (perhaps to premises controlled by states, as is the case with liquor in some regions). Drug sales to individuals can be tracked across dispensaries using the types of software applications currently used to tally sales of abusable prescription drugs (such as opioids) by pharmacies and state agencies. One important legislative initiative would be to limit cannabis advertising, as has been mandated for cigarettes and alcohol at a national level. We saw previously that adolescents are especially influenced by prominent local-dispensary ads. This seems a strong rationale for curbing such advertising. An effective way to discourage some cannabis users from overconsumption could be to tempt them to use smaller amounts of more desirable marijuana. To encourage the growth of niche markets for unique or high-quality cannabis, more costly products would have the aim of cultivating more discriminating consumers who ingest lower overall quantities of THC. Together, these standards and restrictions would have a particular focus on reducing adolescent use and avoiding some of the truly undesirable outcomes I contemplated in the prior chapter.

Improve product quality and ensure uniformity and safety

Currently, cannabis-testing laboratories are not well regulated. Dispensary owners can send product samples to several labs and report the most favorable (usually the highest THC-percentage) results. Enforcing uniform national standards on quality testing for cannabis products will be essential to implement. This effort will entail standard testing of contents in registered laboratories. These constituents would include at a minimum the percentages and amounts of multiple cannabinoids and terpenes, similar to the requirements for pharmaceuticals. To keep everybody honest and accurate, disguised specimens of already-known content would be submitted to the laboratories on a regular basis by a federal agency. This type of procedure is already used as part of the approval process for medical laboratories.

As the Food and Drug Administration mandates for foods, they will also need to implement rigorous safety testing to ensure that cannabis products are free of pesticides, fungi, and heavy metals, which will help protect consumers from harmful chemicals. This safety information should be clearly printed on package labeling in a standard manner. Some states such as Connecticut have “seed-to-sale” laws that track cannabis products at key steps throughout production. A standard universally recognized THC symbol should be prominently displayed. As in Canada, standard health warning labels should be mandated, as they are currently for alcohol and tobacco products. Ideally, this key information would be displayed in large legible type, with content such as “Unsafe for pregnant or lactating women,” and “Do not operate a motor vehicle or heavy machinery for two hours after using this product.” As has been legislated by our neighbor to the north, there should be clear federal rules on packaging and labeling for all forms of cannabis edibles, such as standardizing their form and color, and selling them as individually wrapped portions in clearly marked childproof containers that bear standard warnings. Sales of edibles such as gummy bears, “Krondike Bars,” and THC-infused chocolate, which could easily be mistaken for candy by young children, should be limited.

Dispensaries and point-of-sale procedures

Early in the book, we reviewed the sociology research where dispensaries were telephoned, ostensibly by pregnant women experiencing morning sickness. These pseudo-customers were advised by budtenders that cannabis products were a safe and effective means for treating their condition. Such worrisome results have led many to suggest that legislation may be necessary to bar budtenders from making medical claims or providing medical advice. One extension of this theme would be to have appropriate age restrictions for budtenders, and to train and license them in a standardized manner, as is already required in many states for barbers, cosmeticians, and so on.

In an effort both to control inappropriate mass prescribing by physicians in “pill mills” and to track drug-seeking patients receiving prescriptions from multiple physicians, many states oversaw the creation of a database of controlled substances. Tracking marijuana purchases and issuing medical-cannabis

certificates in a similar manner would help reduce the incidence of abuses, as I mentioned earlier.

Legalization is often followed by the opening of multiple dispensaries. In Boulder, Colorado, there are now more dispensaries than both Starbucks and regular pharmacies. Living close to a dispensary and viewing its advertising increases cannabis use among youth. Thus some legislators have proposed capping the allowable number of cannabis retail outlets in a particular area and limiting or prohibiting the use of dispensary billboards.

Appropriate product pricing

Economic research has shown that pricing is one of the primary drivers behind someone's decision to buy alcohol or tobacco—products comparable to cannabis.[17] For example, in 2018 Scotland set a minimum price on sales of a standard alcohol unit. Thus, in supermarkets and liquor stores, the bottle equivalents of a pint of beer, a shot of spirits, and a glass of wine could not be sold below a set unit price. Within the following year, alcohol sales fell significantly. The corresponding economic equivalent would be to price cannabis based on THC content. Accordingly, decisions on drug taxation and pricing will play an important role in how much cannabis is purchased and by whom. Price too low and you will encourage cannabis overconsumption resulting in, for example, higher dependence rates. Price too high and you will drive consumers back to the black market, with its links to crime and its unregulated, completely untested product. This is a good example of Susan Weiss's dictum that scientific considerations should override commercial ones.[8] The temptation for states is always to push for maximum tax revenues. That should be resisted. How should we adjust pricing to help prevent occasional cannabis consumers from becoming frequent or dependent binge users? The late Mark Kleiman wrote cogently on this issue.[12] There may be a distinct key price point. According to one view, if the US-wide cost of an hour of cannabis intoxication falls below a dollar, then the type of dysfunctional uses that we discussed in Chapter 5 (misguided self-prescribed therapy) begin to spike among vulnerable individuals.[18] This unwanted effect could theoretically be prevented by appropriate pricing. Prices could be adjusted dynamically based on dispensary sales data that tracked consumption rates—all in an attempt to keep consumption in the "Goldilocks zone."

Teaching teens using facts and avoiding inappropriate scare tactics

Credible and effective public education about the potential harms of cannabis use is important, given that consumption increases in those who see marijuana use as harmless. Such education needs to start appropriately early. Teens, with their still-maturing brains, tendencies toward impulsivity and living in the moment, disinclination to think about future consequences of their actions, and feelings of relative invulnerability, are predisposed to try recreational drugs of all types. Use of alcohol and other drugs is relatively common in high schools. Adolescent brains

are still developing, and neural maturational processes such as pruning are disrupted by cannabinoids. These biological facts place teens at increased risk for particular harmful effects of cannabis, including dependence and psychosis. One way of curtailing cannabis use by teens is to educate them about these potential harms, but this is easier said than done. Existing research data provide useful guidance on drug education strategies that succeed and fail. “Just Say No” policies clearly don’t work. The best-known drug education campaign, DARE (Drug Abuse Resistance Education), preaches abstinence and is dramatically ineffective. Former First Lady Nancy Reagan supported government-funded youth antidrug programs, including the infamous “Just Say No” initiative. DARE began in 1983 as the brainchild of the LA police department. Almost $1 billion was spent on this campaign, and it is generally recognized to have been a failure. DARE was undermined by its tendency to make inaccurate and exaggerated antidrug assertions that were easily debunked by savvy kids and by its short-term focus. For example, a 2009 meta-analysis of 20 controlled studies revealed that teens enrolled in the program were no less likely to use drugs than those who had not been exposed.[19–21] One illustration of DARE’s general cluelessness is that it accepted as fact and subsequently mistakenly published on its website an entire satirical report that made numerous outrageous claims regarding cannabis, including: “Four teens become pregnant for every joint smoked,” “Marijuana candies, sold on the street as ‘Uncle Tweety’s Chewy Flipper’ and ‘Gummy Satans,’ are taking the country by storm,” and “Children are being addicted to marijuana. I knew this day would come, when a liberal president allowed a state to legally sell Marijuana Flintstone vitamins to children.”

Exaggerated *Reefer Madness* scare tactics fail to have the intended impact. Most teens are acutely aware when someone is trying to sell them a bill of goods. When in 1986 President Reagan’s drug advisor Carlton Turner suggested that marijuana could make you both gay and more susceptible to AIDS, few adolescents paid attention except to roll their eyes.

So what sort of drug education does work on the school-age individuals who most need to hear science-based information? Also, what is the most appropriate setting to receive this guidance? According to the 2012 National Survey on Drug Use and Health by the Substance Abuse and Mental Health Services Administration, the home front is a good starting point. Teens who consistently learn about the risks of drugs from their parents are up to 50% less likely to use them than those who don’t learn in this way.[22] Middle and high schools are the next obvious places to teach teens the risks. The Drug Policy Alliance has what I believe is a sensible policy on high-school drug education. Reaching high-school students who already have exposure to drugs is a particular priority. A large-scale review suggests that successful programs involve many aspects missing from the DARE approach.[23] Strategies that work include leveraging social influence (for example, using peer leaders), focusing on sustained interaction between students and instructors over a long period, and providing accurate knowledge regarding substance-use norms. For example, it is important to convey that the majority of

students do not use drugs and that student beliefs regarding frequency and quantity of use are significant overestimates. Using role-playing exercises regarding acceptable drug-refusal behavior is helpful in building effective interpersonal skills. Programs with the best track records tried to elicit a commitment not to use drugs from students and explored their intentions not to indulge. Other features that boosted success included additional community interventions and teaching life skills to students.[23]

As well as dealing with cannabis-associated risks in a factual manner, important educational information needs to be embedded in a more general context that might apply to all recreational substances. Teachable skills such as how to avoid social pressures to use drugs, not using them to cope with unpleasant emotions, and stress-reduction techniques are examples. These can help individuals move out of an existing substance use disorder or avoid initial drug entanglement.

We need to design effective courses that will restrict teen cannabis use. In general, we know which approaches and programs work. But funding for effective drug education in schools is not cheap. Mandating drug education in schools paid for by local taxes on cannabis is one obvious revenue source. In Colorado, however, such planning has not played out in the way imagined by taxpayers, who expected more money and more to the education. Evidence of good intent was clearly present initially. For example, a pre-legalization TV ad stated, “Let’s have marijuana tax money go to our schools rather than criminals in Mexico.” In 2017–18, the total marijuana tax revenue for Colorado’s public schools was $90.3 million, or 1.6% of the entire $5.6 billion K–12 public-school budget. Of this tax money, $11.9 million, or 13%, went into substance-abuse and health-related programs.[24] This level of funding sounds respectable, although admittedly we would need more details about the programs themselves and how those dollars were spent to know that for sure. But very few states invest currently in such programs.

In addition to school education programs, there is a need to teach the adult workforce more generally about cannabis-related job safety. We also need to create policies for child protective services regarding their response to positive marijuana screens in newborns and pregnant mothers, post-legalization. Another obvious source of funding for drug education is to divert federal money from the expensive and generally ineffective War on Drugs. According to the Drug Policy Alliance, the United States spends $51 billion annually on this effort. Alan Leshner, a former director of the National Institute on Drug Abuse, pushed consistently for better public drug education, stating that people need to be informed that addiction is “a brain disease expressed in behavioral ways that occurs in a social context.” [25] Leshner also talked about the “great disconnect,” meaning, “the large gap between the public’s perception of drug abuse and addiction and the scientific facts.” [26] Addressing this gap by spreading scientific information more effectively was one factor that helped motivate me to write this book.

Some of the needed adult educational content is obvious: consumers need to know the facts regarding the implications of high THC percentages and THC-CBD ratios, and authorities should be alerting individuals at high risk of psychiatric illness to avoid use. This last priority leads to the next question.

Can we identify individuals at high risk for psychosis and prevent them from using cannabis?

Part of the answer to this question is a practical scientific one. Even if we could come up with an ideal test to identify individuals at high risk from cannabis-related psychosis—for example, a composite psychosis genetic risk score or a brain scan—there is no ethical way to mass screen young people to identify who is at high risk. Neither is screening practical from a budgetary point of view, when the tests may be expensive, the rate of schizophrenia in the population is only 1% to begin with, and not everybody who's identified as being at risk will develop the illness even if they are exposed to cannabis. Additionally, even if all this testing were able to identify individuals who are at substantially increased risk of psychosis, those pinpointed may choose to ignore advice not to use cannabis. A more practical, if less specific, approach is to educate teenagers about the risks of using cannabis, as proposed earlier. So, teach them, don't screen them. Part of that advice could be more focused. That is, if an individual has a family history of schizophrenia or another psychotic illness, or if using marijuana tends to make them feel paranoid, or they have previously experienced a brief psychotic episode when using the drug, then their risk for developing a more serious psychotic illness is likely increased significantly by further cannabis use. Furthermore, if despite being informed of these risks they wish to continue using cannabis, then they can reduce their odds of psychosis by using it as infrequently as possible, by avoiding high-THC-containing formulations, and possibly by picking compounds with more equal THC-CBD ratios. These are all practical and teachable harm-reduction skills.

In addition, teaching high-risk individuals stress-management techniques may offer a degree of protection. The evidence for this comes from a recent Toronto study that measured brain changes in individuals in their early 20s who were at high risk for developing schizophrenia. These young people did not have a clinically diagnosable psychotic illness but had experienced several months of symptoms such as believing that objects in the environment were changed in some way, being suspicious that people might be following them, and experiencing declines in school performance without an obvious explanation. Such people have about a one-in-three chance of ultimately developing a psychotic illness. The Toronto investigators used a PET scanner to measure the release of the neurotransmitter dopamine from parts of the prefrontal cortex in these individuals while they performed a stressful task that involved solving challenging mental arithmetic problems. Nine of the volunteers used cannabis regularly, while 23 had never used. The key finding was that the cannabis-smoking group released much

less dopamine from this part of their brain during the task and showed more psychosis-like symptoms following the stressful math stimulus.[27] The study (despite the relatively small number of subjects tested) is telling us something about a possible biochemical mechanism related to cannabis smoking that might help explain the biology behind their increased risk for schizophrenia and its relationship to stress. As well, the study suggests a practical strategy. Teaching stress-reduction techniques to all pupils (as happens already in some schools) may reduce risk while offering general benefits and boosting life skills.

If we can anticipate a somewhat greater number of cases of cannabis-related psychosis emerging, then we can also plan ahead in terms of harm reduction. There is evidence that early preemptive identification and prompt treatment of psychotic illnesses in young people improve long-term outcomes. Part of the tax dollars derived from marijuana sales can be devoted to addiction treatment programs and to community early psychosis-detection and intervention initiatives. The Australian psychiatrist Patrick McGorry successfully lobbied his government for funds to create and implement a national network of early psychosis intervention and treatment centers that have been widely copied elsewhere. Such steps are cost effective. In addition to this, educational campaigns and public-service announcements aimed at increasing awareness and reducing stigma will help individuals obtain speedy referral to coordinated specialty care programs. For example, simple cognitive behavioral therapy as an add-on treatment seems modestly effective in preventing first-episode psychosis.[28,29] And depending on how future drug trials turn out, CBD may even have a preventative role for at-risk individuals.[30]

Reducing marijuana-impaired driving

In Chapter 7, we discussed at length the considerable difficulties in detecting specific cannabis-related impairment at the roadside and the complexities of establishing recent THC use through blood and saliva testing. Since there is reasonable evidence that recent cannabis use does impair driving, then finding reliable, straightforward, research-based methods for detecting it is on everybody's agenda. Various THC breathalyzer devices would represent a considerable step forward—if they prove as effective as advertised. Other technology to detect impairment at the roadside is under development. Although effective and foolproof roadside testing for cannabis-impaired driving has yet to be realized, effective preventative measures can be implemented now. In New Zealand, controlling driving under the influence of marijuana relies in part on widespread public-safety advertisements. Sample slogans include "Hits lead to hits," and "Grinding one"—next to a picture of a cannabis bud—"can crash the other"—next to a picture of a wrecked automobile.

Changing drug laws and drug policies

Policymakers commonly assume that tougher drug policies reduce adolescent

cannabis use. Alex Stevens is a sociologist and professor in criminal justice at the University of Kent in the United Kingdom who has evidence to dispute this seemingly commonsense view. He recently surveyed over a hundred thousand teens in 38 countries—across Europe and in Russia and Canada—about their cannabis use. Consistent with many prior studies, his work demonstrated no link between tougher cannabis penalties and lower use, even after carefully controlling for differences among both the countries and the participants, for example, in terms of socioeconomic status and national income.[31] So, laws need to be smart rather than tough.

In Chapter 10, I had much to say regarding the need to change current policies on cannabis-related incarceration and to limit the prison industrial complex that informs a continuing need for drug-policy change. One key issue being debated in many states is whether past records for minor cannabis-related convictions should be expunged (restorative justice). A second policy question is whether minority individuals previously convicted of simple cannabis-related possession should be accorded priority when retail licenses for cannabis dispensaries are issued.

Testing for drugs in the workplace

This complex public-safety issue has a vague *Brave New World* feel to it. We have seen that acute cannabis use is accompanied by short-lasting cognitive impairment. Therefore, companies may be rightfully concerned that workers will use the now-legal substance during breaks and may be injured on the job or perhaps damage equipment. Unlike alcohol, cannabis would not be detected on the user's breath or necessarily by obvious intoxicated behavior. In context then, marijuana would be just one drug used recreationally among several that have entered the legal sphere, along with alcohol and abused prescription drugs. So a first step when cannabis intoxication is suspected should not be to determine whether an employee's drug screen shows up positive. As we have seen in the case of driving, toxicology is not particularly informative in distinguishing between recent and days-old marijuana use. The bottom line is to determine whether, whatever the cause, this person is impaired right now in a way that will interfere with his or her job performance. For people with jobs where safety is paramount, such as blast-furnace operators or long-distance truck drivers, some businesses have already journeyed along this path of screening employees' performance. Portable devices exist that can cognitively test a worker at baseline to establish their normal (negative urine tested) sober function scores. Examples of this technology are handheld digital devices that test a subject's focused attention and ability to provide correct answers. Some of these gadgets can communicate results via PC or smart phone from distant sites—for example, from truckers out on the road. The employee can be texted on their smart phone at a random time and asked to test themselves on the device, or he or she can be screened at the beginning or end of a work shift. If their current performance on the device fails to match their sober baseline, then they are required to report for mandatory more

detailed, appropriate assessment. It would be prudent to consider such screening routinely for individuals in skilled jobs with a high public-safety impact, such as train engineers and airline pilots. If this seems harsh, recall that around 1% of airline pilots test positive for cannabis, although admittedly we are not sure how recently they used. You should always ask yourself, “Does the person flying my 747 right now belong to that 1%?”

What are the research issues of the future?

Outside of cannabis-associated risk reduction, there are numerous other interesting topics that research can help address, making them great fodder for future studies. A couple of these are listed below. But it is worth noting that levels of funding for cannabis-based research in general are disproportionately low, scientific investigators’ access to experimental substances is unnecessarily difficult, and existing research has had a hard time keeping pace with emerging public-policy issues. As noted earlier, in August 2023 the US Department of Health and Human Services recommended that marijuana be reclassified from Schedule I to Schedule III within the Controlled Substances Act. If this advice becomes law, then access to cannabis for research purposes will become significantly more straightforward.

Prolonged use of concentrates

For individuals who use dabs and other concentrates in large amounts, the long-term consequences of such super-use are unknown at this point. Because of their relatively recent availability, users haven’t consumed them for long enough yet to reveal anything about their possible long-term side effects on either lungs or brains. Neither have research laboratories challenged subjects with the high THC doses provided by these compounds. Obviously, this type of research needs to be carried out. But THC provided by the National Institute on Drug Abuse, for example, does not yet include these types of concentrated formulations. To what extent significant tolerance to dabs, shatter, and their ilk occurs and how rapidly is unknown. Although concentrate users are increasing in number, it’s likely that future cannabis consumers will also include upscale professionals and hipsters extolling expensive prime craft bud, following the example of current-day wine snobs.

Risks of illicit vaping

In mid-2019, a spate of reports emerged nationwide in the United States and revealed hundreds of cases of serious lung-related illnesses and some deaths related to vaping. Evidence implicated illicit vaping supplies, especially “home-brewed” cartridges used for consuming nicotine and THC, manufactured in underground “pen factories.” It’s relatively straightforward to purchase large quantities of vape pens, empty cartridges, and realistic-looking fake packaging online, either through legitimate or dark-web sources. THC and nicotine liquids

are both readily obtainable, and given a little time and effort, it's straightforward to mix the ingredients together, perhaps cut them with dubious adulterants to increase profitability, and inject them into the individual vape cartridges.[32] All of this assembly is several orders of magnitude easier than, say, the procedures seen in *Breaking Bad*, as no new chemicals have to be synthesized in the pen factory. If you have the skill set to make mac and cheese from a box, then you can probably do a creditable job making a home-brewed vape cartridge. The problem is that some of the carrier material mixed with the drug (particularly the THC) may contain vitamin E acetate, which has been fingered as a potential lung irritant, and additionally other potentially harmful substances. This is an evolving story that may ultimately affect the status of all portable vaping devices in the United States.

New sources of cannabis and cannabinoids

How can we grow better cannabis plants faster and cheaper? Producing larger quantities of cannabinoids at industrial scale to bring down prices will help fuel the discovery of new ways of growing both cannabis and its essential biochemical contents. Significantly scaled-up hydroponic cannabis groweries seem to be one such emerging trend, as we encountered in the previous chapter. Crop scientists are already exploring ways of growing hardy, disease-resistant hemp on a large scale. Geneticists may join them in a quest to produce robust, easy-to-grow cannabis plants that thrive when cultivated en masse outdoors. Traits such as resistance to powdery mildew, auto-flowering and day-neutral maturation, and disease resistance need to be combined in engineered plants to produce predictable THC and CBD ratios. If security measures can be figured out for field agriculture, then outdoor growth of drug-cannabis crops may soon follow. This also reduces the production costs associated with tight environmental controls on indoor grow facilities. Initially desirable crop traits will be engineered by plain old-fashioned plant breeding. But genetics will eventually accomplish this process more precisely and predictably.

In 2011, Canadian biologists published the first cannabis genome by sequencing Purple Kush DNA. Companies such as NRGene are focused on using single nucleotide polymorphism markers (SNPs) to inform them about genetic variation within cannabis plants.[33] Detailed knowledge of this information can be used to help build more desirable chemovars without relying on guesswork or the drudgery of breeding thousands of candidate plants. Another approach is to use genetic techniques directly to custom design marijuana plants that display particular features. For example, CRISPR-cas9 is an enzyme that can be used to cut and edit repeating DNA sequences and to introduce new snippets of DNA into the genome that code for desired features. In the world of botany, CRISPR-based techniques allow highly specific and fine-tuned alteration of a plant without the trial and error associated with most attempts at genetic modification of cannabis. The usual stages of producing novel chemovars include selectively crossbreeding then growing plants to maturity over three to four months and screening them.

This is a slow, laborious trial-and-error process. The precision of CRISPR allows the introduction of new beneficial features (such as disease resistance or increased terpene production) or the removal of undesirable ones (such as small plant size). Yoav Giladi is a plant breeder at the Volcani Center in Jerusalem and an advisor for the Israeli Industrial Hemp Pilot Program who has begun to focus on using these techniques.[34] Finally, geneticists are rapidly discovering the key genes that underlie the synthesis of cannabinoids, terpenes, and other compounds within the cannabis plant. With that knowledge, they can use techniques such as CRISPR both to genetically engineer superior plants or intriguingly to introduce those same genes into yeast or bacteria, which can then be grown on a massive scale in factory vats, bypassing botany altogether.[35] Stay tuned for further developments in these and other areas over the next few years.

The future of medical cannabis

Medical marijuana is at a crossroads. Nearly 10% of cannabis users in the United States report using the drug for medicinal purposes.[7] Strong claims are made for its utility in treating a variety of medical conditions, but solid evidence of its efficacy is mostly lacking, for a variety of reasons we've examined in prior chapters. How can we move the field forward?

Cannabis, as we've learned, is a complicated plant, containing many different classes of chemical compounds, with numerous compounds within each class, although we tend to oversimplify things by referring to medical cannabis as if it were a single entity. Research studies have already shown us that CBD is effective in significantly reducing the frequency and severity of certain types of infantile and childhood epileptic seizure syndromes. And there is preliminary evidence that various cannabinoids, including THC and terpenes, have neuroprotective, anti-inflammatory, pain- and spasm-reducing, appetite-increasing, and tumor-suppressing properties. But as I've stressed, much of the needed evidence for medical marijuana's real-world effectiveness, based on properly powered and adequately controlled clinical trials, is still lacking. That situation needs to change. Current circumstances don't imply that constituents of cannabis don't work to treat various illnesses. We don't know that yet. What they do suggest strongly is that we need to begin carrying out such studies as soon as possible. Clinical trials need to be designed as rigorously as is practicable to begin providing definitive answers. And in order to do that, the first crucial step is for the federal government to reclassify cannabis from its current Schedule I status and make it significantly easier for researchers to access these compounds. One of the first issues that needs addressing is how real and how significant entourage effects are.

If recreational marijuana becomes federally legalized, then individuals who wish to purchase cannabis to treat medical complaints can do so as they wish. Presumably the distinction between medical and recreational forms of the drug will diminish. Medical insurance is unlikely to ever cover medicinal cannabis in the form of flower or edibles, but it may ultimately pay for standardized tinctures

or pure compounds extracted from the herb. It's those purified compounds that I next want to talk about.

The pharmaceutical deployment of plant-based medicines—such as the heart drug digitalis, derived from the familiar garden foxglove; the 1950s blood-pressure drug reserpine, extracted from an East Asian herb; and the anti-malaria drug artemisinin, from the traditional Chinese wormwood plant—tends to follow a similar pattern. First, a traditional herbal medicine or initial lab experiments screening novel flora may suggest that a particular plant is useful in helping to treat a specific medical condition. Then pharmacologists and chemists extract multiple candidate compounds from the plant and home in on the relevant one, often using animal experiments. These scientists then purify this identified chemical and turn it into a potential medication with known properties that can be dosed precisely when prescribed to patients. Next, they figure out how to synthesize it, then run the compound in clinical trials to prove real-world effectiveness. If those trials show that the drug meets the FDA's criteria as both safe and effective, then they will market it. With cannabis, in most cases we're at the very start of that long process. The plant contains multiple compounds, including hundreds of cannabinoids, terpenes, flavonoids, and many others that may have potential medical properties. Beyond that, these ingredients may also rely on entourage effects to produce optimal medical results when used in combination. The relevant plant constituents and combinations may well differ for treating different disorders. So as the first step, scientists need to examine the vast library of compounds locked up inside the cannabis plant and then figure out which compounds are most effective in treating which illnesses. We know that the cannabis chemical library is huge, but it is not infinite, and modern drug screening protocols can efficiently pick it apart and establish which compounds work best in which situations. On the other hand, as outlined elsewhere in the book, pharmaceutical companies may well skip the cannabis plant altogether and decide their best strategy is to proceed with drugs that act on the endocannabinoid system directly, such as FAAH inhibitors and CB receptor modulators. Another reason why the medical and recreational drug paths are destined to diverge is that smoking and vaping are probably not the most effective delivery mechanisms for any medicinal drug.

What can we learn from Canada's experience?

What Canada can teach us is a question that is already occupying social-policy researchers and epidemiologists, and it is beginning to yield lessons about the consequences of legalization in the United States. In June 2018, Canada fully legalized recreational cannabis, the only country other than Uruguay to make this transition. Adult Canadians and people visiting the country can purchase marijuana at stores throughout the nation and online. The launch began by allowing sales of cannabis flower, seeds, and tinctures. A year later, it followed up with sales of concentrates and edibles. Canada has very strict rules regarding

cannabis sales; some people have compared these more to the marketing of tobacco than that of alcohol. Canada adopted several legal provisions to constrain use. These laws have sharp teeth. For example, they prohibit production or sale of products that appeal to youth, particularly through packaging or labeling. They do not allow cannabis sales through vending machines or self-service displays. Violation of these prohibitions results in fines of up to $5 million or 3 years in jail. Giving or selling cannabis to a person under 18 is punishable by up to 14 years in jail, as is "using a youth to commit a cannabis-related offense." [36] Possession of small amounts of cannabis over the statutory limit is merely ticketed, but possession of large amounts can land you up to 5 years in jail. Cannabis-impaired driving is taken seriously and punished appropriately. Cannabis products are packaged analogously to European cigarettes, in plain, unenticingly colored, industrial-style boxes, plastered with large-font health warnings. Containers for edibles are childproof and bear highly visible warning labels. Advertising is limited and kept away from children.

This legislation varies to some extent from province to province. For example, in Ontario, consumers are free to smoke or vape marijuana anyplace they can legally use tobacco, but in other provinces such as Manitoba there are hefty fines for the same behavior.[37] Ontario initially planned to sell cannabis only at government-run stores but then changed its mind and switched to private licenses. The minimum age for purchase varies from province to province; federally it is 18 years, but Quebec set the limit at 21 years. There have been calls for expunging the record of individuals who had been previously criminalized for cannabis possession; so far there's been little progress on this front. And while employers are still debating how to handle positive-THC drug tests, the police are wondering how to deal with the persisting black and gray markets. Meanwhile, in Ottawa swarms of lobbyists are appealing to the government to loosen the rules.[38]

I discussed many of these Canadian initiatives earlier in this chapter. An important question that public-policy experts are still debating is whether these regulations are sufficiently stringent to reduce harms, or overly harsh and thus encouraging illicit use. For these reasons, keeping a careful eye on drug-use trends over the border will provide us with useful information on how future cannabis legislation should be handled in the United States. Each time a society sanctions the use of a recreational drug, it is implicitly making a series of calculations. From time to time this calculus needs to be revised, and decisions revisited. So it is currently with marijuana. Hopefully emerging policies will benefit from the consideration of existing science. Five years after Canada's nonmedical cannabis legalization, researchers took a close look at the available data. As the authors write, "At this stage, cannabis legalization in Canada appears not to have been the public health disaster anticipated by some of its opponents, but it cannot be described as a comprehensive or unequivocal public health success either." [39] For example, prevalence of cannabis use, numbers of cannabis-related emergency-department visits and hospital admissions, and incidents of cannabis-impaired driving have increased (as expected) or remained unchanged. There have been

significant reductions in arrests and charges related to cannabis use and possession. The prevalence of cannabis use among youth and perceived access to cannabis by minors have remained stable. Pregnant women are using cannabis more. More young children are showing up in emergency departments with unintended cannabis poisoning after ingesting edibles. Two-thirds of cannabis users now buy their product from legal sources. Researchers continue to monitor key acute and long-term health effects, such as rates of cannabis use disorder, emergency-department visits, and chronic lung disease.[39]

In conclusion, while many individuals can use cannabis without problems, cannabis use is not risk free. Existing research can already help mitigate potential harms associated with use of the drug and impact those problems that will increase following likely federal legalization of recreational marijuana. Credible public education can play an important role in harm reduction, particularly given the increases in public perception of cannabis as a harmless substance. This education will enable informed decisions about safe and sensible use. It can be funded through cannabis tax revenues. Policies to protect youth from a burgeoning cannabis industry allied with Big Tobacco and Big Alcohol will be essential. Research-based information about potential problems associated with cannabis use should be conveyed to educators and to medical and psychiatric providers. This will help deal with genuine risks while avoiding panic and alarmism. State and national policymakers will need quick and ready access to relevant research data to help them formulate laws and regulations. Still, it is wrongheaded to think the only choices we have in drug policy are a punitive approach centered exclusively on enforcement or one based on careless or ill-considered legalization. Neither has ever worked well. Finally, continued research is necessary to explore the still-large number of unknowns surrounding this ancient and fascinating plant.

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