pulling weeds

David Casarett used to just say *No* when his hospice and palliative-care patients asked about using medical marijuana as a treatment or to relieve their symptoms. After researching and writing his new book, *Stoned*, his answer is "a lot more nuanced."

BY KATHRYN LEVY FELDMAN

PHOTOGRAPHY BY CANDACE DICARLO

Down the hall from the staff kitchen, where a tray of freshly baked chocolate chip cookies releases an enticing aroma, David Casarett, director of hospice and palliative care for the University of Pennsylvania Health System, pulls a chair up to the bedside of a 71-year-old patient.

"Tell me what you are thinking," he prods.

"I grew up with an invalid grandmother," she begins haltingly. "She was a vegetable—and I apologize for that phrase, but there is no other way to describe it. She was unable to chew her own food, or swallow." The patient describes the vacuum cleaner that her father rigged up to extract the pieces of pre-chewed food that still managed to get caught in her grandmother's throat and how her bed linens had to be changed multiple times each day.

"This went on for eight years, and I vowed, at that time, that I would never go through that again. It was not what she was going through; it was what it did to the whole family," she continues. "I don't want to be like that. When I was in the hospital two months ago, they had tubes literally rolling from side to side. I was no longer capable of eating, of drinking, of choking. I was my grandmother."

Casarett listens for more than 30 minutes to his patient's memories about her family, her last hospitalization, a near-death experience, and her desire to "go gently into the night." He sums up what he thinks she has told him and offers assurance that he and his team can help her develop a plan so that she doesn't end up like her grandmother, or in a nursing home if that's not what she wants, or even back in the hospital. "What you are asking for is something we can help you formulate," he says. "You can go home with a plan."

In the hall, Casarett is quick to point out that not all bedside conversations in this 20-bed inpatient unit at the Hospital of the University of Pennsylvania (HUP), where he does his clinical work, are as lucid and coherent as this one. But most do involve concerns about being a burden to others, loss of dignity, and the desire to avoid pain.

If Casarett had his way, these discussions would take place long before palliative-care practitioners are called in for a consultation, or patients reach the end of their lives. (For some insight on why they don't, see page 29.) One reason he became a palliative-care physician, he says, is that it offered "some of the biggest opportunities to change the healthcare system."

"David is all about vision; he's the big-picture guy," says Nina O'Connor, who directs palliative care at HUP.

Casarett came to Penn in 1998 as a fellow in palliative medicine, after earning his bachelor's degree from Swarthmore College and a master's and MD from Case Western Reserve University. He joined the faculty the following year, serving as medical director of palliative care at Philadelphia's Corporal Michael J. Crescenz VA Medical Center, teaching in the division of geriatrics in the Department of Medicine, and serving as a fellow at the Center for Bioethics, Institute on Aging, and the Leonard Davis Institute of Health Economics. In 2007, he was named director of research and evaluation of Penn's hospice and palliative-care program, and has been program director since 2011.

Casarett has done extensive research on end-of-life issues, and he has also written three nonfiction books for a general audience: *Last Acts* in 2010, about the choices people make at the end of life; *Shocked* in 2014, about the science of resuscitation ["Expert Opinion," Jan|Feb 2015]; and *Stoned: A Doctor's Case for Medical Marijuana*, which came out in July.

In the early days of his career, a dying patient asked Casarett what he should do with the remainder of his time. His lack of a satisfying answer dogged him enough to write *Last Acts*. *Stoned* was also sparked by a conversation with one of his patients (a retired Penn English professor, he says).

"She asked me if medical marijuana could help her with some of her symptoms from advanced cancer," he recalls. He replied with the "stock answer [we] learned in medical school," which was that marijuana was illegal in Pennsylvania and that there were no medical benefits.

But that patient pushed back. "She had even found some randomized controlled trials, and I realized she knew more about the benefits than I did," he says wryly. "It occurred to me that, as a palliative-care physician, I needed to learn more—and probably the rest of us needed to learn more, too."

Casarett did not set out to make a case for medical marijuana, but to "state the facts on both sides to lead to a more informed dialogue," he says. "For me, the best medical writing involves going on a journey, and a willingness to test your assumptions, make mistakes, and, above all, to be surprised by what you find."

It was a combination of scholarly rigor and writing skill that brought Casarett to Penn in the first place. He'd published an article in *The New England Journal of Medicine* that caught the eye of Janet Abrahm, former chief of the division of adult and palliative care at Dana-Farber Cancer Institute and Brigham and Women's Hospital and professor of medicine at Harvard, who at the time was on Penn's faculty. Among her responsibilities was directing HUP's palliative care fellowship program.

"*Stoned* is about the science of marijuana," but the book has a broader message about "dissatisfaction with the health care system."

In the article, Casarett asked clinicians whether they would "honor" a Do Not Resuscitate (DNR) order that they themselves had obtained from the patient. "He offered the physicians three different clinical scenarios and asked in each one whether they would resuscitate the patient despite the DNR order," Abrahm recalls in an email. "I was intrigued by the wit and sophistication of the study and by the analysis of why a significant number of physicians would resuscitate someone … even though they themselves had ascertained from patients that they would NOT want to be resuscitated."

Casarett's paper and their subsequent conversations "convinced me that David would make important contributions to

palliative care and ethics." In his later work, Casarett has continued to "elucidate the whys, not just the whats of our practice, and the ethical assumptions that underlie (or should underlie) the assumptions we make," she adds.

Still, she didn't necessarily expect that he would "write for a lay audience," let alone devote a book to a drug that is still illegal under federal law.

But while the book's conversational, first-person tone should help it reach a larger public—especially among those who might "pick up a book on a topic they previously hadn't considered," Casarett says—the careful scientist stands behind every word, documenting the physiology of molecules and receptors, evaluating the results of clinical studies, and analyzing evidence and outcomes.

"*Stoned* is about the science of marijuana," Casarett notes, but the book has a broader message as well: about "dissatisfaction with the healthcare system."

Medical marijuana is currently legal in 23 states and the District of Columbia. In DC and four states—Washington, Colorado, Oregon, and Alaska—adults can also use cannabis recreationally. According to "America's Weed Rush," a 2015 report produced by the Carnegie-Knight News21 initiative, legalization efforts could appear on ballots in about a dozen more states (including Pennsylvania) next year.

New Jersey and Delaware, where many Penn Health System patients reside, are among those 23 states, notes Susan Kristiniak, a nurse and associate director of palliative care at Penn. "Many of their care modalities require an understanding of the use of medical marijuana. Our formal group, under David's initiative, started looking at this about a year and a half ago, just thinking about what we needed to know because of the situation in New Jersey."

Complicating the picture, however, is the decades-old federal prohibition of the sale and use of marijuana, which is classified by the Drug Enforcement Administration as a Schedule I substance, "with no currently accepted medical use and a high potential for abuse." Until that changes, according to Casarett, "it's going to be impossible to create national rules about how [marijuana] can be used, prescribed,

HOSPICE AND PALLIATIVE CARE AT PENN

In 1982, the US government instituted a hospice funding benefit for Medicare patients (most over age 65) with terminal illnesses and a prognosis of six months or less. According to the National Hospice and Palliative Care Organization, hospice involves "a team-oriented approach to expert medical care, pain management, and emotional and spiritual support, expressly tailored to the patient's needs and wishes. Support is provided to the patient's loved ones as well."

Hospice care is not curative and may be provided in a patient's home or a dedicated hospice center; it may be delivered by the patient's personal physician, hospice physician, nurses, home health-aides, social workers, trained volunteers, and clergy. The irony of providing this comprehensive level of care only to patients who are at the end of their lives is not lost on David Casarett, who directs Penn's hospice and palliative-care program. "The Medicare hospice eligibility criteria—having a prognosis of less than six months and a choice of comfort care—significantly limit hospice access for patients who could benefit," he says.

Though "many of the clinical skills overlap," palliative care is broader than hospice, according to Casarett's colleague Nina O'Connor, who runs the program at the Hospital of the University of Pennsylvania. She describes palliative care as "specialized care for any patient with a serious, life-limiting illness, even patients who are still undergoing aggressive treatment. "Many of our patients are cured or recover," she says. "On the other hand, some of our patients ultimately transition to hospice. We help patients decide what kind of care is right for them."

Inpatient palliative care is a consult service provided to patients who require an extra layer of support and symptom management. "Most physicians can handle 80 percent of pain and symptom management, but there's that 20 percent that's really difficult," O'Connor explains. "The difficult symptoms are what we focus on." Patients who might need palliative care include those with cardiac conditions or advanced lung disease, or who are enrolling in a clinical trial, waiting for an organ transplant, or undergoing an aggressive course of chemotherapy.

HUP's palliative-care team includes six doctors, five nurse practitioners, two social workers, one nurse, a dedicated chaplain, and a pharmacist. There is an outpatient palliative-care clinic at the Abramson Cancer Center. "We talk about everything: goals, spirituality, social support, and symptoms and management," O'Connor says.

In general, palliative-care physicians spend a lot of time with their patients—about one-and-a-half hours in the initial consult, on average. "Some would argue this is what every physician should be doing at every patient encounter, but it is incredibly time-consuming," she adds. "I think that the struggle for practicing physicians is that the time is not do-able."

As demand has increased, it's becoming a challenge for Penn's palliative-care teams to serve all their patients. They were following about five patients per day when the program officially began in 2013; the number is now up to between 50 and 70 per day. They actually had to cap their consults this past spring. "It's been overwhelming in terms of the number of people seen," Casarett says. "But the response and growth of palliative care at Penn Medicine is incredibly positive."

Alana Sagin, a palliative-care physician, credits a large share of that growth to the leadership of Casarett and O'Connor, who "made [Penn] a great place to do this work." Penn's medical community has a solid understanding of palliative medicine, "and are very welcoming and accepting, and need our services all the time," she adds.

"It's very clear to me that a big part of our success is their outreach and advocacy, especially someone like Dr. Casarett, who has a very high profile, is well known, and advocates well for us."

That view is echoed by Gloria Chriss, a nurse-practitioner who works in the palliative-care program Casarett helped establish at Philadelphia's VA hospital near the Penn campus. Casarett approaches "the study and practice of palliative care with the focus on evidence and outcomes," she writes in an email. "His scholarship is recognized throughout the palliative world, and he is definitely one of the most influential specialists who has developed standards of care, particularly in end-of-life goal setting and structuring family and patient discussions." *—KLF*

and distributed." The law also significantly limits the types of controlled randomized studies that might generate data to substantiate or debunk marijuana's efficacy.

When he was doing the research for *Stoned*, Casarett spent most of his time in California and Colorado—states where medical marijuana is legal and plentiful—visiting dispensaries and talking to patients who use marijuana and physicians who prescribe it. Most were more than willing to share their views. "A lot of [them] have been arguing for the benefits of medical marijuana for decades," he says. "They were not opposed to a physician, who began very skeptical, hearing about its benefits."

Casarett also searched for "high-quality published studies," tracked down researchers who are doing that work, investigated how marijuana gets into one's system, and even documented his own experience smoking a joint to relieve back spasms.

What he found surprised him.

"When I started this project, I did not think marijuana had any medical benefits at all," he admits. "But I have been reassured that it does have benefits, and I don't think there's much doubt about that in my mind."

Marijuana, as a medicinal herb, has been around for thousands of years. Its biologically active components include several dozen cannabinoid molecules. The most prevalent of these, and the ones about which the most is known, are tetrahydrocannabinol (THC) and cannabidiol (CBD). THC makes you feel stoned and sometimes sleepy or paranoid; CBD tones down these effects. Casarett likens them to Don Quixote and Sancho Panza: one tilts at windmills; the other does his best to "prevent him from doing too much harm to himself or to windmills."

The ratio of THC to CBD in medical marijuana is important when it comes to treating specific conditions. Barth Wilsey, director of the University of California, Davis's Analgesic Research Center and an anesthesiologist by training, has done considerable research on the use of marijuana for neuropathic pain, which is often very difficult to treat. Many patients use marijuana with high levels of THC to get relief, but Wilsey believes that CBD may prove to be just as effective.

"Wilsey tells me that his studies have pushed THC levels lower and lower," writes Casarett. "Initially he used marijuana that had a THC concentration of 7 percent, then he reduced that to 3.5 percent, and then to as low as 1.3 percent. In each subsequent study, he found as much pain relief but fewer psychological side effects." Evidence also suggests that a combination of THC and CBD can reduce some of the symptoms of multiple sclerosis, like muscle stiffness and spasms, and perhaps slow the progression of the disease.

Marijuana is also effective in treating nausea, especially the kind induced by some forms of chemotherapy. It turns out that this is an area of research in which there are studies dating back to the 1950s, and according to Casarett, "the weight of the evidence is pretty clearly on marijuana's side." And even in patients who are losing weight because of conditions such as AIDS or cancer, unrelated to nausea, the drug does increase appetite, which in itself is worth something. "Everyone knows marijuana gives you the munchies," Casarett writes. "If your family sits down to dinner every night, eating means you get to participate."

So clinical evidence exists for marijuana's effectiveness in treating neuro-

POT OF GOLD?

With medical marijuana legal in almost half the states, recreational use permitted in a handful plus the District of Columbia, and more states seeming likely to move toward some form of legalization, many observers see the industry as a lucrative business opportunity, even given the numerous remaining legal issues and regulations that vary from one state to another. Among those vying to make their mark are two Penn alumni, Ted Rebholz WG'05 and Shanel Lindsay C'03.

Oakland-based Rebholz is an entrepreneur, adviser, and investor in the legal cannabis sector. Since January 2015, he has been president of Temescal Wellness, Inc., which holds two of the four medical-marijuana licenses in New Hampshire, where medical marijuana became legal in 2013.

The New Hampshire business, which will cultivate marijuana, manufacture numerous cannabis-infused products, and operate two dispensaries to serve qualified New Hampshire patients, is the first of several initiatives planned under the Temescal Wellness brand. But while the company will "incubate and fund multiple start-ups in the industry," Rebholz says, the primary focus is to "help qualified patients obtain the right type of cannabis and the right type of delivery system for their conditions."

Rebholz pursued a social-entrepreneur track at Wharton, and says he is motivated "not only by the financial rewards but by the need to help my fellow man." He's worked in the cannabis industry since 2010, as a consulting chief financial officer for Harborside Health Center, which runs dispensaries in Oakland and San Jose. Prior to that, he was founding CFO of Beyond Meat, a health-food company, and of WhipTail Technologies, a data storage company that was sold to Cisco for $415 million in 2013.

Kris Krane—former associate director of the marijuana-legalization advocacy group NORML and currently co-founder and managing partner of 4Front Advisers, which works to professionalize the marijuana industry—calls Rebholz "quite possibly the smartest guy in the cannabis industry."

Among the keys to navigating the state-by-state landscape of licensing regimes, says Rebholz, is reversing the stigma and skepticism "born of a three-generation campaign against the plant based on misinformation," recruiting and training talented operators to model responsible business practices, and forging teams of experienced cannabis operators and local business leaders.

Despite the challenges, he sees cannabis products as a "great way to break into the industry today," and hopes that "disciplined producers emerge to raise the bar for consistently high-quality products that exceed consumers' expectations for dosing, labeling, efficacy, and taste."

Shanel Lindsay wants to be one of those producers.

After majoring in anthropology at Penn, Lindsay, a Massachusetts native, earned her law degree from Northeastern University. She worked as a civil litigator for the Boston

pathic pain, spasticity in multiple sclerosis, and nausea; in addition, there is anecdotal support for a range of conditions including seizures, PTSD, diarrhea, constipation, joint pain, palpitations, depression, diabetes, inflammation, cancer, ALS, AIDS, PMS, sports injuries, fibromyalgia, anorexia, arthritis, migraines, glaucoma, and chronic pain. The list is as long as the strains of marijuana available for purchase to be smoked, inhaled, or consumed.

(Regarding the matter of delivery method, Casarett notes that it takes longer to feel the effects of ingestibles than smoking a joint or breathing in the vapors from a machine or e-pen. This is something patients should keep in mind before reaching for another marijuana-laced brownie or cookie, to avoid having a greater impact than intended when the drug's effect does kick in.)

I suggest to Casarett that the entire process of obtaining medical marijuana involves an uncomfortable level of uncertainty. In many states, getting a medical marijuana card requires multiple visits to a registered physician for treatment of a specific list of conditions and limits your cash purchase to one or two ounces a month. But after all that oversight, patients are left wondering how to decide which marijuana to buy, how to take it, and how often. And who is doing the prescribing?

Very often it is the dispensary, and some are better than others.

"I'm convinced that many people who are curious about it have used it or are thinking about using it, and that's important because I want them to use it correctly."

In the book, Casarett visits one of the sketchier ones—a dispensary "noticeable mostly for its anonymity," featuring a "sign that looks as though it could be taken down in a matter of minutes." Though not a California resident, he easily obtained a letter of recommendation from a doctor, who looked "at least ninety years old" and wore a "rumpled white coat [with] brown stains at the cuff and collar," and whose office was conveniently located in the back room of this clinic. (To be clear, Casarett never did—nor planned to—purchase any medical marijuana.)

The patient experience at Compassionate Sciences Alternative Treatment Center, located right across the Delaware River from Philadelphia in Bellmawr, New Jersey, is very different. The state allows use of medical marijuana for 13 conditions (including severe or chronic pain and severe nausea or vomiting only if a symptom of cancer or HIV/AIDS). To obtain a medical marijuana card, patients must register their alternative treatment site

firm of Sugarman, Rogers, Barshak & Cohen, and in 2010 became employment counsel and director of human resources for the Massachusetts State Lottery. But these days she devotes her time and energy to Ardent, LLC, the Boston-based company she founded in August 2013 whose website describes it as a "biotech and medical device company with pioneering technologies that drastically improve cannabis administration and effectiveness."

The inspiration for the company was Lindsay's personal experience with medical cannabis, which she has used for more than 10 years to treat pain and inflammation caused by an ovarian cyst. "I had used marijuana recreationally and read that you could use it topically to treat pain," she says. She began to process medical marijuana to create her own tinctures, creams and oils; the more she experimented, she says, the more she realized how important decarboxylation—the process by which the marijuana is heated and made biologically available—is to the preparation of consistent, precise doses of medical cannabis.

The problem is that without a precise method for heating cannabis, most of it literally goes up in smoke. Most important, there's also no way to precisely control dosage amounts, leading to inconsistent reactions. Over the years, Lindsay became adept at preparing her own compounds, which proved effective at alleviating her pain. She also became convinced that others could benefit from having access to a simple way to process the plant into sterile, accurate doses.

When Massachusetts passed its medical cannabis law in 2012, Lindsay commissioned scientists at MCR labs to test, refine, and perfect the decarboxylation process and focused on the benefits of sublingual—that is, under the tongue—delivery. The result of her efforts is the NOVA machine, billed as "the first cannabis medical device that allows patients to achieve pharmaceutical grade dosing using the cannabis plant."

"You put the raw plant in the machine, put the cover down and push the button," explains Lindsay. "If you know the composition of the plant before it went in, you know what it is when it comes out, and there is no waste." Patients can then load their own sublingual capsules with the precise dose of the exact strain of cannabis that works for them, with no irritation to the lungs. The NOVA also increases the availability of the cannabinoids in the plant for those who prefer to vaporize, smoke, consume, or make tinctures from the plant, she says. "The idea is that patients need a mechanism to have control."

While the company sells only to medical-marijuana patients in legal states, as a founding member and vice-chair of the Northeast Cannabis Coalition, Lindsay is an ardent advocate for cannabis legalization on the East Coast. "My hope is that legalization of medical as well as recreational cannabis (for those over the age of 21, just like alcohol) keeps moving forward," she says. *—KLF*

with the state and have a relationship with a state-approved physician for at least four months prior to registering. They also must submit proof of identity and residence, and pay a $200 registration fee before setting foot in the door.

Once through that door, however, they enter a clean and professionally run facility, with patient conference areas, educational materials, and an array of product displays and information. All the strains of medical marijuana sold on site have been grown on the premises and tested by the state, and have bar-coded labels.

Patients still rely on staff recommendations as to which marijuana strains might work best for their condition, but the dispensary places a high priority on education. "We provide every new patient with a lengthy consultation about their medicine choices," says Gretchen McCarthy, dispensary director. The staff is available to work with patients to develop a treatment plan based on their symptoms. "We provide patient logs to track performance and our mantra is *Start low and go slow*."

This kind of personalized attention is what patients are seeking from the medical marijuana industry, says Casarett, and on some level from the healthcare system in general. "A lot of people are voting with their feet, saying 'I'd rather manage my own health in an unpressured way.'" At an upscale medical marijuana dispensary, he notes, "people take the time to talk with you, and they listen. You can spend time with other patients learning from them. It's one-stop shopping, which people really like, as opposed to waiting in a clinic waiting-room for an hour to see a doctor for five minutes, getting a prescription (that requires you to go to another place to fill it), and then getting booted out the door."

And as for that unknown dosage and strain best suited to your condition? According to Casarett, it's really not so different from how doctors prescribe pain medication. "For many drugs there are standard doses that work for everybody, but when you are talking about symptom management, that often doesn't work," he explains. "So if you think about marijuana as a symptom management drug—which it kind of is—it's off-putting to people who want to know very precisely what the dose is, but for those of us in palliative care, we generally start with one drug and increase the dosage, watch for side effects, look for benefits. Managing symptoms with marijuana follows exactly the same trajectory that we follow in the managed pain program in palliative care."

Often with fewer side effects: for one thing, you can't overdose on marijuana. "You might get confused, anxious and/or paranoid, but you can't fatally overdose the way you can on opioids," says Casarett. Plus, the effect is relatively short lived. "People are turning to medical marijuana for many of the same reasons people turn to herbal remedies—partly for control and the feeling that it is safer," says Casarett. "And it is in some ways, although keep in mind that opium comes from poppies. Just because it is a flower doesn't mean that it is safer."

And there are dangers as well. First, according to Casarett, medical marijuana users need to be counseled about the risk of dependence or, more rarely, addiction. "If you've got a standard rate at which people become dependent [on a drug], the more people using it, there are definitely, predictably, almost inevitably going to be more people out there who are dependent, and I don't think anyone's thought about how to manage that," he advises. "Providers need to know how to recognize marijuana dependence and dispensaries need to be careful about dependence and be able to screen for it."

Second, as with alcohol, marijuana and driving are a bad combination. "In general, when people are stoned, they know they're stoned, and there is actually important data from states where medical and recreational marijuana are legal, that indicates traffic accidents have gone down," he notes. "But that said, don't go near a car until the marijuana wears off."

Third, there are a number of circumstances in which the use of medical marijuana is contraindicated, such as for patients with coronary artery disease or a history of schizophrenia, and for women who are pregnant. There is a rare condition called hyper-emesis, in which people who use marijuana regularly experience severe nausea. "There should also be education about potential side effects and dosing, just as there is for any other medication. And there should be enough testing so that users have a pretty good idea of what they're using," he writes.

All that said, Casarett's answer to patients' questions about medical marijuana is "a lot more nuanced" now. "I still say it's illegal in Pennsylvania, and I can't give you a recommendation," he says, "but the evidence seems to suggest it could be effective for [a variety] of conditions. I'm convinced that many people who are curious about it have used it or are thinking about using it, and that's important because I want them to use it correctly."

It's been an eye-opening journey from skepticism to appreciation of the benefits of medical marijuana, but Casarett says he's still traveling. "Much to my surprise, I find that I'm much more enthusiastic about legalizing medical marijuana than I was a year ago," he writes. "Not because it always works, because it doesn't always. Nor is it always safe. But, more widespread use, with careful safeguards and monitoring and testing, could let us learn a great deal. Much faster than we ever could if we rely solely on randomized controlled trials."

The decades-long national War on Drugs has made funding clinical research on marijuana extremely difficult, so Casarett and some Penn students set up a Kickstarter campaign (marijuanaresults.org) to see if they could crowd-source marijuana research. That effort failed to meet its funding goal, and the project was pulled on August 21, but Casarett still sees the idea of crowd-sourcing research as "potentially valuable … if there's a way to make sure that those crowds are well-informed and safe."

The bottom line is that anecdotes do matter. "If you have 1,000 people saying marijuana works for Parkinson's disease, those are still 1,000 stories, not randomized controlled trials," he notes. "But if you are a researcher trying to figure out the high-priority target for a clinical trial and you have two reports of the benefits of marijuana for Parkinson's and 1,000 for childhood seizures, maybe you should do a seizure trial because that's where the evidence is pointing. If that's what people are using it for, it's really important to know whether it works or not. Because if it doesn't work, then the 1,000 people who think it works are wrong."◆

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