Marijuana on Trial

Is marijuana a dangerous drug or a valuable medicine?

By KATHLEEN FACKELMANN

For decades, the debate over marijuana's role as a medicinal drug has waxed and waned. The conflict intensified recently, when voters in California and Arizona passed measures allowing seriously ill people to obtain marijuana, with a doctor's OK, for medical purposes.

Lined up on one side of the debate are retired Army General Barry R. McCaffrey, President Clinton's drug policy advisor, and others who believe that marijuana is first and foremost a hazardous, illegal drug. Joseph A. Califano Jr., president of the National Center on Addiction and Substance Abuse at Columbia University and former Secretary of Health, Education, and Welfare, summed up that viewpoint in an op-ed piece published in the Feb. 17 Washington Post. Noting marijuana's reputation as a drug that can lead to hard-core drug addiction, he writes that "teens who smoke pot are 85 times likelier to use drugs such as cocaine than those who have never done so."

Squaring off against the zero-drug-tolerance crowd is a mix of people, including some scientists and patients, who believe marijuana has proven medicinal properties. Jerome P. Kassirer, editor-in-chief of the NEW ENGLAND JOURNAL OF MEDICINE, joined this side with an impassioned editorial in the Jan. 30 issue. "Thousands of patients with cancer, AIDS, and other diseases report they have obtained striking relief from these devastating symptoms by smoking marijuana," he writes. "The alleviation of distress can be so striking that some patients and their families have been willing to risk a jail term to obtain or grow the marijuana."

The passage of the medicinal marijuana laws late last year prompted federal officials to hold a press conference at which Attorney General Janet Reno warned that physicians who prescribe marijuana could be prosecuted under federal law.

Kassirer says in his editorial, "I believe that a federal policy that prohibits physicians from alleviating suffering by prescribing marijuana for seriously ill patients is misguided, heavy-handed, and inhumane."

At present, marijuana is classified under the Controlled Substances Act as a schedule I drug, one that has no medical value and may prove addictive. Kassirer and other advocates want the federal government to reclassify marijuana as a schedule II drug, one that physicians can legally prescribe, despite its potential for

addiction. Morphine is an example of a schedule II drug.

Last month, the National Institutes of Health stepped squarely into the vortex of this maelstrom. Its National Institute on Drug Abuse (NIDA) had assembled an advisory panel to review the scientific evidence on the medical use of marijuana. The 2-day meeting, held on the NIH campus in Bethesda, Md., was marked by scientific presentations, bomb-sniffing dogs, security guards, and outspoken activists.

After hearing the reports, the eight-member panel of scientists concluded that marijuana does show promise as a treatment for certain conditions. The panel singled out marijuana's role as a treatment for the nausea and vomiting that accompany chemotherapy for cancer; the loss of appetite and weight that strikes some people with AIDS; and the high ocular pressures that characterize glaucoma, an eye disease that, if untreated, can cause blindness.

Panel chairman William T. Beaver of the Georgetown University School of Medicine in Washington, D.C., says the panel hopes to deliver a report to NIH this month or next.

The federal government and the advocates agree that one component of marijuana has an accepted medical use.

In 1985, the Food and Drug Administration approved a synthetic version of the active ingredient in marijuana, delta-9-tetrahydrocannabinol (THC). This schedule II drug is marketed by Roxane Laboratories of Columbus, Ohio, under the trade name of Marinol (dronabinol). It was approved to combat the nausea and vomiting that can accompany chemotherapy.

There's a substantial body of published research on THC's ability to ward off such queasiness. "THC clearly has [antinausea] effects in cancer chemotherapy," says Richard J. Gralla, director of the Ochsner Cancer Institute in New Orleans. Gralla gave a presentation at the NIH meeting.

In contrast, "there's not a great deal of data on inhaled marijuana," he notes. The marijuana studies that have been done often contain flaws, he states. For example, a 1988 study of 56 chemotherapy patients revealed that 78 percent received some relief with marijuana. Yet this study didn't include a control group, Gralla says.

It is difficult to design a double-blind, controlled marijuana study, researchers say. Most patients realize that they've received a dummy cigarette and so know they're in the placebo group.

Overall, Gralla says, the data suggest that marijuana, which contains THC, does offer a hedge against nausea and vomiting caused by chemotherapy. Is it as effective as the conventional drugs prescribed by cancer specialists? Gralla's answer is no.

He says that drugs available today offer many cancer patients complete freedom from nausea and vomiting. That's an efficacy marijuana would have a hard time beating, he suggests.

Kevin B. Zeese, an attorney and president of Common Sense for Drug Policy,

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says Gralla has previously testified on behalf of the Drug Enforcement Agency (DEA), which opposes changing marijuana's status. DEA says the push to legalize marijuana for medical purposes will lead to a greater acceptance of it as a recreational drug.

Zeese says it's true that other drugs are available for cancer patients receiving chemotherapy, but he and other advocates contend that some patients can't take those drugs—or any drug, including Marinol, that must be swallowed. In such cases, unrelenting vomiting may lead patients to drop out of a potentially lifesaving chemotherapy regimen, he says.

Advocates also contend that marijuana cigarettes are more effective than the government-approved pills. They say, and some pharmacologists agree, that inhalation delivers a therapeutic dose almost immediately, enabling patients to regulate the amount of the substance they receive and to stop before they experience any psychoactive effects.

Pills, on the other hand, deliver a standard dose of THC. That means some patients get too much, which creates anxiety, fearful imaginings, and other undesirable side effects, and other patients don't receive enough of the active ingredient to alleviate their symptoms.

In 1992, FDA approved Marinol for a second medical use. The agency gave the nod to physicians who prescribe THC in pill form for AIDS patients who suffer from a wasting syndrome.

Some people with AIDS lose 5 to 10 percent of their body weight, a drop that intensifies HIV's assault on the body's infection-fighting abilities, says Kathleen Mulligan of the University of California, San Francisco.

The weight loss often occurs after an AIDS patient suffers from an infection, such as pneumocystis pneumonia. The accompanying feeling of malaise takes away the pleasure of eating, Mulligan said at the NIH meeting. In fact, the patient may never regain his or her appetite. The next time an infection strikes, the person's weight plummets again. Such a loss can prove deadly for an AIDS patient. "People who lose weight die faster, particularly people with depleted levels of lean tissue," Mulligan says.

There's no doubt that THC can revive a flagging appetite.

A study detailed in the *Physicians' Desk Reference* (1994, Montvale, N.J.: Medical Economics Data Production Co.) concludes that Marinol is effective. Researchers enrolled 139 AIDS patients with wasting in a double-blind, controlled study of dronabinol. Half got dronabinol capsules, and the remainder received dummy pills. The researchers found that, compared to the placebo, dronabinol significantly improved appetite in AIDS patients. The study also noted a trend toward weight gain. Unfortunately, researchers don't know whether the spark in appetite is enough to result in a long-term weight gain for AIDS patients.

There have been no studies of marijuana's safety or efficacy in the treatment of AIDS-associated wasting, Mulligan points out.

Glaucoma is a disorder caused by excessive pressure in the eye. Paul Palmberg of the University of Miami School of Medicine, one of the NIH panel members, described a patient with glaucoma who has been using marijuana for 21 years. "There's no question that it's worked," he said at the NIH meeting. With regular use of marijuana and a conventional glaucoma drug, the woman reduced the dangerous pressure in her eyes. Neither approach worked effectively by itself, Palmberg says.

That woman is one of eight patients in the United States who have permission to smoke marijuana legally. Starting in 1976, the government gave a few glaucoma patients, who had not benefited from conventional therapy, permission to use marijuana. No patients have been accepted since 1992, when the program was discontinued.

Despite several favorable testimonials, the scheduled speaker on glaucoma at the NIH meeting presented a negative view of marijuana's role in this disease. Paul Kaufman of the University of Wisconsin Medical School in Madison noted that animal studies on glaucoma and THC have failed to yield consistent results.

Palmberg counters by saying that human studies in the 1970s and 1980s showed THC's efficacy in reducing glaucoma's punishing pressure on the eye. However, researchers at that time discounted marijuana's role in the treatment of glaucoma, supposing that patients would need to experience a high in order to gain any therapeutic benefit.

That assumption turns out to be false, Palmberg says. Regular users of marijuana develop a tolerance for the psychoactive effects of THC but still get relief from their symptoms, he said.

Scientists have yet to figure out how marijuana lowers pressure in the eye, says Kaufman. This makes some scientists uneasy about its widespread use as a treatment for glaucoma.

One of the most intriguing areas of marijuana research addresses a variety of disorders that provoke spastic movements. There is very little data from human trials in this field, said toxicologist Paul Consroe of the University of Arizona College of Pharmacy in Tucson at the NIH meeting. However, laboratory investigations have yielded some tantalizing hints about a natural marijuana system in the human body.

Previous research showed that marijuana receptors, specialized proteins that serve as docks for THC, are clustered in regions of the brain known to play a role in movement disorders such as Huntington's disease. These receptors also bind to anandamide, a marijuanalike substance manufactured by the body (SN: 2/6/93, p. 88).

Consroe and others believe the anandamide system may play a role in regulating muscular movements. If so, could THC help tone down the spasms suffered by people with Huntington's disease, spinal cord injuries, and other disorders?

That's the $64,000 question—and scientists can't answer it just yet. The research so far provides mixed results about marijuana's potential use in treating these disorders.

A 1986 study by Consroe and his colleagues, for example, showed that cannabidiol, a nonpsychoactive component of marijuana, calmed the abnormal movements of five people suffering from dystonia, a rare condition characterized by muscle spasms that contort the body. Yet a 1991 study by the team failed to demonstrate any improvement when people with Huntington's disease took the same agent.

Consroe points out that cannabidiol is just one component of marijuana. In an interview with SCIENCE NEWS he said that his scientific design focused on cannabidiol, rather than marijuana, in part to allow federal funding. "I'm dealing with stuff that's safer than tap water," and it still took years to get the research approved, he says.

This isn't the first time that researchers, politicians, and patients have argued the merits of marijuana as an herbal remedy. In 1988, SCIENCE NEWS interviewed Robert Randall, one of the patients who smokes marijuana for glaucoma that didn't respond to conventional

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medication (SN: 2/20/88, p. 122.)

Randall says he's still smoking marijuana legally, but in the intervening years he unwittingly embarked on a scientific study of sorts.

In 1994, Randall was diagnosed with late-stage AIDS. For a year, because his health was deteriorating, he stopped smoking marijuana. "From April of '95 to '96, I didn't use marijuana, and in that period of time I lost more eyesight than I had in the previous 20 years," he recently told SCIENCE NEWS.

Randall's weight also slipped during that period, from a healthy 170 pounds to 125. In April 1996, his doctors put him on the new antiviral drugs called protease inhibitors. Many HIV-infected people can't tolerate these drugs because they cause extreme nausea. Randall turned back to marijuana.

He now weighs 180 pounds, and his eyesight has stabilized. He credits marijuana for the improvement.

"There's experience out there," Beaver says. "But it is difficult to figure out how you can tap this in any meaningful way." For example, Randall's story, no matter how compelling, remains far from a scientific study.

Drug companies can't patent marijuana, so there's no incentive for them to conduct such trials, says Lester Grinspoon of the Harvard Medical School in Boston. He and other researchers have called on NIH to support such trials. However, they point out, a single institute has quashed marijuana trials in the past.

"The National Institute on Drug Abuse—the only legal source of marijuana for research—has been blocking clinical trials by refusing to provide marijuana to FDA-approved studies," says the Washington, D.C.-based Marijuana Policy Project.

Two letters published in the Sept. 7, 1995 NEW ENGLAND JOURNAL OF MEDICINE support that contention. In one, Grinspoon and his colleagues said that NIDA derailed an FDA-approved trial of marijuana proposed by Donald I. Abrams of the University of California, San Francisco.

The proposal was the first in more than 10 years to include marijuana in its design. In a second letter, Abrams and his colleagues expanded on Grinspoon's letter, saying that they had worked extensively with FDA staff to design their study. After getting FDA approval, NIDA spent 9 months reviewing the proposal, a period during which Abrams got no feedback from NIDA or the DEA, which also opposed the project.

In April 1995, NIDA abruptly rejected the proposal.

Such reports have created a chilling effect, at least when it comes to marijuana research. Government opposition has made it "impossible to do those kinds of studies," Consroe says flatly. Indeed, he says, most scientists simply won't submit a marijuana research proposal, even though it may be scientifically sound.

"It's like jumping off the Brooklyn Bridge," he says. "You know what's going to happen."

Will the panel's report help change NIH's attitude toward marijuana research? It's anyone's guess right now. The panel had a very limited mission: to review the existing data on medicinal marijuana. The group was also charged with identifying areas that might merit further study. It remains to be seen whether NIH will use the panel's report to justify funding clinical trials of marijuana.

Meanwhile, Abrams says, thousands of AIDS patients in the San Francisco area alone are already using marijuana—without any assurance of its safety or efficacy.

The last speaker at the NIH meeting, FDA's Robert Temple, alluded to the difficulties in resolving this issue. Noting that passions on both sides of the debate are running extraordinarily high, he warns: "This isn't going to be easy." □

Behavior

Hunches pack decisive punches

You gotta know when to hold 'em, know when to fold 'em—but keep in mind that an ounce of intuition trumps a pound of pondering, hands down.

That's the implication of a new study in which people tried to make money, or at least not lose their shirts, by discerning whether four decks of cards were stacked for or against them. Insightful players rapidly accumulated unconscious knowledge about the riskiness of selecting cards from each deck, based on mental updates of their picks' monetary values, neuroscientists report in the Feb. 28 SCIENCE. That information was then applied intuitively to improve their choices.

Good judgment relies on the brain's unobtrusive records of prior events in uncertain situations, from the poker table to the board room, contend Antonio R. Damasio of the University of Iowa College of Medicine in Iowa City and his coworkers. Conscious reasoning often arises as an afterthought to intuitive knowledge and the bodily reactions it evokes, such as sweaty palms or flushed skin, the scientists theorize.

They studied six patients who had suffered a kind of frontal-brain damage that spares general intelligence and memory but causes social and decision-making problems (SN: 5/21/94, p. 326). Ten people with intact brains served as controls.

Participants received a stash of phony money and four decks of cards placed facedown. They then turned over 100 cards from the tops of the decks in an attempt to find cards that netted cash rewards and to avoid cards that carried cash penalties. Picking cards mostly from two of the decks would result in an overall loss, and selecting mostly from the other two would yield an overall gain.

Questioning of the players after their first 20 selections and then after every 10 picks revealed that the controls began to favor the money-making decks well before they could articulate a strategy for choosing cards. In contrast, the six patients continued to select a large number of cards from the losing decks, even after they had figured out the most financially promising strategy.

Lowered skin resistance to a mild electric current—a bodily sign of anxiety—occurred in controls as they pondered choosing cards from the riskier decks, even before they were consciously aware of which decks to avoid. Patients showed no such anxious undercurrents, either before or after identifying the riskier decks, possibly reflecting their inability to form or exploit an intuitive perspective on the task. —*B.B.*

Prospects for beating bulimia

People suffering from bulimia nervosa, most of them women, usually try to hide their repeated bouts of binge eating and purging. So it comes as no surprise that scientists know little about the long-term prospects for recovery, either on one's own or after various types of treatment with psychoactive drugs and psychotherapy.

A statistical synthesis of existing data on this topic, published in the March AMERICAN JOURNAL OF PSYCHIATRY, suggests that about half of the women initially diagnosed with bulimia shed their symptoms completely after 5 to 10 years, whether they get treatment or not. Another 20 percent of the women still display the disorder, while the rest exhibit problems with bingeing and purging that fall short of a formal diagnosis of bulimia.

Bulimia treatments may speed the recovery of women who would stop bingeing and purging on their own after 5 to 10 years, suggest Pamela K. Keel and James E. Mitchell of the University of Minnesota in Minneapolis. Nonetheless, in the first 4 years after an initial diagnosis, about one-third of those who recover experience a relapse, the researchers report.

The analysis combined 88 studies that tracked a total of 2,194 bulimic women for 6 months to 10 years. —*B.B*