



campuses, with each building's cost exceeding \$150 million. Then come the operating expenses.

When Feldmann began directing Health Canada's BSL-4 lab in Winnipeg, Manitoba, he was cautioned by C. J. Peters to keep his operating funds separated from his research funds. While at USAMRIID, Peters went through a cold winter and the heating bill ate up much of the lab's money. Unless a laboratory has long-term research goals and government support, like UTMB, said Feldmann, many entities considering building and operating a BSL-4 facility will find the costs prohibitively high.

The University of California at Davis is one of a handful of finalists bidding to win a grant for an NIH-funded high-containment lab, and Murphy says that work at the Davis facility will focus on a mix of diagnostics and research, such as vaccine development. The researchers will also study therapies designed to ameliorate the biochemical cascades triggered within the body by viral disease.

Pharmaceutical companies long ago gave up on research involving

What Makes A "Special" Pathogen So Special?

Only certain pathogens are deemed deadly enough to require the extremely sophisticated safety features of a biological safety level 4 (BSL-4) laboratory. The main criterion is that the pathogen is associated with a high fatality rate. Thus, the coronavirus that causes severe acute respiratory syndrome (SARS), which has "only" a 5% to 7% mortality rate, is handled under BSL-3 conditions.

A second consideration is whether there are approved treatments. With so many antibiotics available, this rules out bacteria, so that only viruses without vaccines are generally considered BSL-4 material. One exception to this is smallpox. Even though smallpox researchers are vaccinated, most of the general population is not. Thus, for security reasons, the pathogen is handled only under high-containment conditions at the CDC's BSL-4 facility.

Another exception to the rule: anthrax spores that could cause inhalational anthrax. Because anthrax spores (when inhaled) can act so quickly that antibiotic treatment may be ineffective, material containing spores is handled in a BSL-4 facility. Those infected with most BSL-4 viruses have few options, primarily the antiviral ribavirin and plasma transfusions from survivors of the specific virus.

these viruses, finding them too expensive to study with too little potential for profit. But Murphy says that September 11 changed everything and pharmaceutical companies started expressing interest once the federal funding faucets started flowing. Researchers also feel that while the funding was made available for bioterrorism response, there will

be a public health payoff in an increased capacity to deal with emerging viruses.

"Many of the pathogens have not received biomedical interest in recent years, so there is a lot to do," said Murphy. "And to be able to do research, and then switch over to diagnostics during an emergency, is what our country needs." □

Medical Marijuana Center Opens Doors

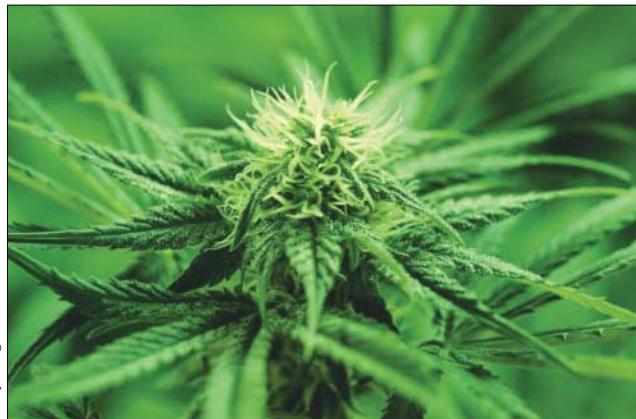
Brian Vastag

WHILE SCIENTISTS FUNDED BY the National Institutes of Health (NIH) have scrutinized marijuana's effects on the brain, lungs, and other parts of the body over the past 2 decades, there has been virtually no research into the drug's therapeutic potential.

That changed last year, when the Center for Medicinal Cannabis Research (CMCR) launched its first clinical trials. Interest in the issue was sparked by the 1996 legalization of medical marijuana in California, and fanned by two influential reports—

the first from an NIH consensus panel (*Workshop on the Medical Utility of Marijuana*. Bethesda, Md: National In-

stitutes of Health; 1997), the second from the Institute of Medicine (IOM) of the National Academies (*Marijuana*



Although scientists have studied marijuana's effects on the brain, lungs, and other parts of the body over the past 20 years, there has been little research into the drug's therapeutic potential.



Medical Activists Push to Relax Marijuana Scheduling

The Drug Enforcement Agency (DEA) is reviewing a petition to move marijuana out of the agency's most restrictive category, drugs with a "high potential for abuse" and "no known medical use."

Filed by the Coalition for Rescheduling Cannabis, the petition cites 220 journal articles to support its position that marijuana's medical value should move the drug from Schedule I, which includes heroin and morphine, to Schedule III, which includes drugs that have an accepted medical use but also "some potential for abuse."

Frank Sapienza, the DEA official in charge of the review, said that the process is "legally and scientifically rigorous." After internal review, the DEA can dismiss the petition or send it to the Department of Health and Human Services (DHHS) for detailed scientific scrutiny, although the DHHS recommendation is nonbinding. If the petition is rejected, anyone can request an administrative hearing. But even if the administrative judge recommends rescheduling, the DEA still has the final say about the matter.

The petition argues that the DEA is not following federal scheduling guidelines, in particular the section calling for drugs to be scheduled according to relative abuse potential. According to the Institute of Medicine, 23% of those who try heroin become dependent (as defined in the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition*), as do 17% of those who try cocaine, a Schedule II drug. However, only 9% become dependent after using marijuana (*Marijuana and Medicine: Assessing the Science Base*. Washington, DC: National Academies Press; 1999).

Sapienza said that with marijuana, "it's not that those studies [on relative likelihood of dependence] are rejected, but you have such a long history and so much actual abuse. So we would tend to look at actual abuse instead."

On another front, Congress is considering a bill to reschedule marijuana; 25 members of the chamber voiced their support for the measure, considerably fewer than are needed to move the bill forward.—B.V.

and Medicine: Assessing the Science Base. Washington, DC: National Academies Press; 1999).

FIVE CLINICAL TRIALS

Now, the medical marijuana research flame is carried by two University of California campuses, a dozen researchers, and five clinical trials that will ultimately enroll 450 patients. Physically housed at the neurobehavioral human immunodeficiency virus laboratory at the University of California, San Diego, the CMCR published its first journal article earlier this year, a meta-analysis of long-term cognitive effects of marijuana. In it, CMCR Director Igor Grant, MD, and colleagues conclude that there is no "substantial, systematic effect" of long-term, regular cannabis consumption on the brain. Six of eight brain functions measured—attention, abstraction, perception, verbal skills, motor skills, and reaction

time—did not differ between marijuana smokers and nonsmokers. The other two, learning and forgetting, displayed "very small but discernible negative effects" (*J Int Neuropsychol Soc*. 2003;9:679-689).

"Real life" impacts of such small effects are likely negligible, said Grant, which is a bit of good news for medical marijuana proponents. "Short- and long-term prescriptions, if things ever came to that, are going to be reasonably safe, as far as neurological effects go," Grant said. (The Institute of Medicine report concluded that smoked marijuana's effect on the immune system is unknown; that chronic use "might lead to acute and chronic bronchitis"; and that although there is laboratory evidence that marijuana smoke is carcinogenic, "[t]here is no conclusive evidence that marijuana causes cancer in humans.")

While the meta-analysis begins to address the safety issue, the center is also

collecting hard data from a safety trial of smoked marijuana. Other clinical trials are testing marijuana for muscle spasms in multiple sclerosis, neuropathy in AIDS, and pain in cancer.

Each trial is conducted by University of California researchers in San Diego or San Francisco; the CMCR acts as coordinator. The aim, said center codirector Andrew Mattison, MD, is to free physician scientists from the regulatory shackles that bind such controversial work.

PASSING AGENCY MUSTER

To reach viability, each proposed study survives a scientific and bureaucratic gauntlet. After passing muster with scientific advisory panels at the CMCR, and at the state and federal levels, a proposed protocol requires approval from the US Food and Drug Administration (FDA), the National Institute on Drug Abuse, and the Drug Enforcement Agency (DEA). Each plays a different role: the FDA approves experimental research; NIDA supplies marijuana via the agency's farm in Mississippi; and the DEA monitors distribution to physicians and patients.

In Mattison's words, the center is fortunate to have "cultivated very collegial relationships" with senior staff at each agency, smoothing the way for distribution of the marijuana cigarettes smoked by patients.

Still, the process is "very complicated and time-consuming. A lot of it is transportation and handling issues," Mattison said.

SECURITY ISSUES

To pass DEA muster, the program must provide locked safes, adequate ventilation, secure transportation, and a host of scales to weigh the arriving, dispensed, and smoked product—that is, the ashes, which Mattison said he collects at the behest of the DEA. (A DEA official, however, denied that the agency requires investigators to retain the ashes).

Research with smoked marijuana—provided as cigarettes of varying po-



tency for dose-escalation studies—is the first phase of the center’s three-tiered plan. Stage two involves development of nonsmoked delivery systems, such as a mucosal spray under study in the United Kingdom. The ultimate goal, stage three, is to invent new molecules that interact with the body’s built-in cannabinoid receptors.

Mattison describes this as a natural progression, normal pharmaceutical development with an abnormal starting point. After filtering the legal and sociological baggage associated with marijuana—a heavy load to be sure—the process boils down to basic botanical drug development.

To pick one of many examples, “people used to chew a plant called foxglove for heart trouble,” Mattison said, referring to the source of digitalis. But unlike that example, marijuana contains over 400 active compounds. The primary psychoactive ingredient, Δ^9 -tetrahydrocannabinol, was approved by the FDA in 1985 as an antiemetic for cancer patients; in 1992, the agency added AIDS-related anorexia as a second indication. Sold as dronabinol, and taken orally, the pills take up to an hour to exert their effect, whereas smoked marijuana has discernible effects in 20 to 30 seconds. Cancer patients have reported trouble keeping the pills down.

Besides more effective delivery, Mattison said that the other compelling reason for studying smoked mari-

Bush Wants Medical Marijuana Ban; Canada Begins Selling

The Bush administration has asked the Supreme Court for permission to strip medical licenses from physicians who discuss medical marijuana with their patients, a move in sharp contrast to a new Canadian plan to distribute the drug.

In October, a California appeals court cited First Amendment free speech protections when it barred federal investigation or sanction of physicians who discuss or recommend marijuana for patients. The administration wants to overturn that ruling, arguing that it interferes with the US Drug Enforcement Agency’s obligation to protect the public.

Medical marijuana is most often used by patients with AIDS wasting syndrome, chronic pain, nausea from chemotherapy, and muscle spasticity from multiple sclerosis. Since 1996, eight Western states (Alaska, Arizona, California, Colorado, Hawaii, Nevada, Oregon, and Washington) and Maine have legalized medical use of marijuana.

Meanwhile, Canadian Minister of Health Anne McClellan announced that her government will begin selling marijuana to licensed patients. The interim policy was developed after an Ontario court ruled that because the government had authorized medical marijuana, it was obligated to provide a safe source. Grown under contract in an abandoned underground mine in Manitoba, marijuana will be sold in 30-g packets at cost, which is about three to five times cheaper than typical street prices.

Canada legalized medical marijuana in 2001; as of July, 582 people were authorized to possess or cultivate it.—B.V.

juana is that many other active ingredients may eventually prove useful. Drug companies, for instance, have shown interest in cannabidiol, a possible soporific. Scraping pharmaceutical gems from the cannabinoid ore will take considerable patience.

The CMCR may not have that much time. Initial state funding, approved by the California legislature, is running dry, leaving Grant and Mattison scrambling for resources.

Negotiations with the FDA and a pharmaceutical company might bear fiduciary fruit, but the researchers ultimately need to secure a steady stream of grants from the NIH, a tricky task.

“With cannabis research you have to have not only excellent study design but excellent pilot work” to win federal funding, said Grant. “The State of California took a real chance on this. We’re going to get them some answers.” □

Addendum: Volunteer Opportunities Overseas

IN THE AUGUST 7, 2002, ISSUE OF JAMA, Medical News & Perspectives published its triennial list of Physician Service Opportunities Overseas (pages 559-565), giving the

names of groups through which physicians may offer medical service abroad—almost always in developing countries. Subsequently, the following organization requested to be added to

the list. Copies of the original list are available free from Gwenn Gregg, who may be reached by telephone at (312) 464-5204 or e-mail at gwenn_gregg@jama-archives.org. □

Organization/Location	Contact/Phone/Fax/E-Email/Web	Area Served	Specialties Needed
Free Rural Eye Clinics, Inc 2194 Heywood Circle Oregon, WI 53575	Guillermo de Venecia, MD tel (608) 274-5769 fax (608) 274-5769 e-mail: gdevenicwisc.edu Web: http://www.frec-sight.org	Philippines	Ophthalmology