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## Is Pot Good For You?

By John Cloud / San Francisco

I never smoked pot in junior high because I was convinced it would shrivel my incipient manhood. This was the 1980s, and those stark this-is-your-brain-on-drugs ads already had me vaguely worried about memory loss and psychosis. But when other boys said pot might affect our southern regions, I was truly terrified. I didn't smoke a joint for the first time until I was 21.

By 12th grade, about half of young Americans have tried marijuana, which put me in the geeky other half. I used to think this was a good thing, since I never developed a taste for pot and avoided becoming dependent. But as the medical-marijuana movement flowered and weed's p.r. improved, I often wondered if I shouldn't have relished it as a kid, before I had a personal trainer to tsk-tsk my every vice. Shrinking testicles? Mushy brains? I came to see these as grotesqueries invented by antidrug propagandists.

It turns out that the study of marijuana's health effects is at once more complex and less advanced than you might imagine. "Interpretations [of marijuana research] may tell more about [one's] own biases than the data," writes Mitch Earleywine in *Understanding Marijuana: A New Look at the Scientific Evidence*, published in August by Oxford. For example: "Prohibitionists might mention that THC [delta-9 tetra-hydrocannabinol, the smile-producing chemical in pot] often appears in the blood of people in auto accidents. Yet they might omit the fact that most of these people also drank alcohol. Antiprohibitionists might cite a large study that showed no sign of memory problems in chronic marijuana smokers. Yet they might not mention that the tests were so easy that even a demented person could perform them."

The science of marijuana--especially its potential medical uses--is malleable because it's so young and so contradictory. Although preliminary data are promising, scientists haven't definitively shown that the drug can safely treat nausea or pain or anything, really. Some experts claim the U.S. government has sabotaged medical-marijuana research, and there is evidence to support them. Even

so, in the past few years scientists have made rapid advances in their basic understanding of how Cannabis sativa works. By 1993, researchers had found the body's two known receptors for cannabinoids, the psychoactive chemicals in the plant (THC is the main one, but there are at least 65 others). Since then, there has been important new work in several fields that users, potential users and former users should know about--and that voters should take into account before deciding whether to legalize pot.

So much new research has appeared that in November the *Journal of Clinical Pharmacology* and the National Institute on Drug Abuse will publish a 100-page supplement devoted entirely to marijuana. The *Journal* gave *Time* an advance look; it's a comprehensive review that will annoy both sides in the drug war. You won't find clear evidence that pot is good or evil, but the research sheds light on some of the most important questions surrounding the drug:

### Can it kill you?

No one has ever died of THC poisoning, mostly because a 160-lb. person would have to smoke roughly 900 joints in a sitting to reach a lethal dose. (No doubt some have tried.) But that doesn't mean pot can't contribute to serious health problems and even DEATH--both indirectly (driving while stoned, for instance) and directly (by affecting circulation, for example). A paper published last year in the *journal Angiology* found 10 odd cases in France of heavy herbe smokers who developed ischemia (an insufficient blood supply) in their limbs, leading in four cases to amputations. It's not clear that marijuana caused the decreased blood flow, but the vascular problems did worsen during periods of heavy use. Another 2001 paper, in *Circulation*, found a nearly fivefold increase in the risk for heart attack in the first hour after smoking marijuana--though statistically that means smoking pot is about as dangerous for a fit person as exercise.

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### Does it make you sick?

Marijuana may directly affect the immune system, since one of the body's two known receptors for cannabinoids is located in immune cells. But the nature of the effect is unclear. A recent study showed that THC inhibits production of immune-stimulating substances. But cigarette smokers may do greater harm to their immunity than pot users, who tend to smoke less. A study published earlier this year found that tobacco smokers but not marijuana smokers had high levels of a type of enzyme believed to inflame the lungs. Dr. Donald Abrams, professor of clinical medicine at the University of California, San Francisco, found that short-term cannabis use doesn't substantially raise viral loads of HIV patients. (People with HIV sometimes smoke marijuana to stimulate appetite.) In fact, his study participants who smoked pot enjoyed significantly higher increases in their lymphocytes (cells that help fight disease) than those who took a placebo.

### **Can it give you cancer?**

Data on cancer also generate mixed conclusions. A 1999 study of 173 patients with head and neck cancers found that pot smoking elevated the risk of such cancers. (Smokers of anything should also worry about lung cancer.) But it's not clear that THC is carcinogenic. The latest research suggests that THC may have a dual effect, promoting tumors by increasing free radicals and simultaneously protecting against tumors by playing a beneficial role in a process known as programmed cell DEATH.

### **Is it addictive?**

Those who believe you can't become physically or psychologically dependent on marijuana are wrong. At least three recent studies have demonstrated that heavy pot smokers who quit can experience such withdrawal symptoms as anxiety, difficulty sleeping and stomach pain. On the other hand, the risk of becoming dependent on marijuana is comparatively low. Just 9% of those who have used the drug develop dependence. By comparison, 15% of drinkers become dependent on alcohol, 23% of heroin users get hooked, and a third of tobacco smokers become slaves to cigarettes.

### **Does it make you stupid?**

Potheads are dumber than nonusers, but only a little. Earlier this year, the Journal of the American Medical Association published a study of 102 near-daily marijuana users who wanted to quit. The authors found that the longer subjects had toked up, the worse their memories and attention spans. But they were hardly like Gobi, the Saturday Night Live wastoid who is so ruined he can barely talk. Participants who had used cannabis regularly for an average of 10 years fared significantly worse on only two of 40 indices of cognitive functioning (they had particular trouble estimating how much time had passed during a test). Those stout folks who had been smoking pot for an average of 24 years did significantly worse on 14 of the tests. But scientists can't say that marijuana causes such problems. "These long-term users may have been worse off in the first place, before they ever smoked marijuana," says Dr. Harrison Pope, a Harvard psychiatrist who wrote an editorial accompanying the study arguing that "we must live with uncertainty" on whether pot causes long-term cognitive impairments.

### **What about sex?**

The latest studies suggest I needn't have fretted so much about pot's gonadal consequences. "Marijuana might interfere with [kids'] ability to go through puberty," says Dr. Adrian Dobs, co-author of a paper on the endocrine effects of the drug in the upcoming Journal of Clinical Pharmacology. "But the abnormalities seen are not really clinically significant." Despite tales of male potheads growing breasts, the long-term effects on adult glands are uncertain.

### **Do the sick really benefit?**

So if marijuana can be harmful to healthy people--but usually isn't--could it actually be good for the

sick? This is where the science gets scraggier--and in the absence of data, politics takes over. What we know is that healers have accumulated copious anecdotes on weed's powers over the past 4,700 years. Understanding Marijuana author Earleywine credits a (possibly mythical) Chinese emperor with introducing the plant as a treatment for gout around 2700 B.C. But the emperor also thought his pot potion would help memory, making him the first of many fans to aggrandize the drug's medical potential. The ancient Greek doc Galen even used the drug to treat flatulence.

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The A.M.A. issued a report last year summarizing the body of knowledge about medical marijuana. It's shockingly slim. Dr. Abrams in San Francisco has produced some of the clearest evidence to date of pot's therapeutic value. Even though his clinical trial was designed merely to investigate whether marijuana is safe for hiv patients, he also turned up data that anyone who ever had the munchies already knew: pot makes you hungry. Test subjects who smoked marijuana gained an average of 6.6 lbs. during the trial, compared with 2.4 lbs. for the group taking the placebo. Some other findings from the A.M.A. report:

#### **NAUSEA**

Patients who are HIV-positive or undergoing chemotherapy can have trouble keeping food down, so anything that helps them eat is significant--though not necessarily for the reasons marijuana boosters think. Pot's ability to enhance appetite may have more to do with its high and less to do with any direct effects on nausea. Only 20% to 25% of patients in two 1980s trials could completely control vomiting with marijuana; other drugs work better for emesis. Still, the A.M.A. recommended more studies on marijuana for those who don't respond to the other drugs, and it notes that for those feeling sick, inhaling a substance may be more palatable than swallowing a pill.

#### **GLAUCOMA**

Marijuana does reduce pressure on the eyeball, about 25%, but the drug isn't always practical as a glaucoma treatment. Many who have the disease are elderly and can't tolerate pot's tendency to raise heart rates.

#### **SPASTICITY**

Marijuana can help people with spasticity (extreme muscle tension) and tremor due to multiple sclerosis and trauma. But the drug hasn't been rigorously compared with the standard antispastic treatments.

#### **PAIN**

In patients with postoperative pain, THC is more effective than a placebo, and some reports suggest

smoking pot may reduce the need for highly addictive opioids. But the A.M.A. says better-designed studies are needed to properly evaluate pot as a painkiller. Several are under way. In California, five teams of researchers are conducting studies of marijuana as an analgesic, particularly for cancer and nerve pain.

The A.M.A. concludes that the lack of "high-quality clinical research ...continues to hamper development of rational public policy" on medical marijuana. Which raises the question, Why, after five millenniums, doesn't such research exist? Two possible answers: First, the government may have rejected cannabis studies to avoid any challenge to its view that pot is dangerous and medically useless. Second, pot may just be dangerous and medically useless.

The drug wasn't always so controversial in the scientific establishment. The U.S. Pharmacopeia, a doctors' listing of remedies begun in 1820, first included cannabis in 1870. The Pharmacopeia didn't drop pot until its 1942 edition, the first published after cannabis was outlawed in 1937. Eventually most physicians began to view the drug as little more than a crude intoxicant. They tended to favor new-fashioned drugs that were refined by pharmaceutical firms into pure chemicals. Raw marijuana contains some 400 compounds.

It wasn't until the '70s that modern methods were applied to test the medicinal effects of cannabis. As Earleywine recounts, a UCLA study designed to confirm police reports that pot dilates pupils found instead a slight constriction. That's how doctors discovered the drug could help glaucoma sufferers by reducing intraocular pressure. In the years after that discovery, 26 states opened therapeutic research programs.

But the Federal Government, which by then controlled the only legal supply of marijuana, had just passed the Controlled Substances Act of 1970. That law placed marijuana in Schedule I, the designation for drugs without valid medical use. State health officials found it difficult to persuade their federal counterparts to give them cannabis for research, as doing so would undermine the law, at least in spirit, by suggesting there were medical uses. (Only seven states got pot. One was Tennessee, which is why Al Gore's sister was able to try the drug before losing her battle with lung cancer in 1984.)

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Then, in 1985, the Food and Drug Administration (FDA) approved dronabinol, an oral form of synthetic THC, to treat chemotherapy-induced nausea. Many doctors believed dronabinol, marketed as Marinol, could provide the benefits of the plant without the impurities. By the mid-'80s, the availability of Marinol and the escalating drug war had killed the state research programs. But

Marinol turned out to have shortcomings. Because it enters the blood through the stomach, it doesn't work as fast as smoked marijuana. Because it is essentially pure THC, its users can get too high. "Marinol does tend to knock people out," says Abrams, the San Francisco doctor who has conducted trials with both Marinol and pot. "Our patients [taking Marinol] spent a lot of time in bed, and that wasn't the case with those smoking marijuana."

Such problems appeared in only "a small portion of the patients in our clinical trials," says Dr. Hjalmar Lagast, a vice president for Solvay Pharmaceuticals, which makes Marinol. He notes that the drug comes in three strengths, allowing doctors to pick the right dose. By the early '90s, at the height of the U.S. aids epidemic, many patients so preferred marijuana to Marinol that they would use the street drug regardless of legality or safety. Abrams and a few others began pushing the government to permit new studies of marijuana to find out what these patients were doing to themselves.

Officials again resisted, and some researchers became convinced the government would never allow evidence of pot's possible benefits to emerge. In 1999, Paul Consroe, a professor of pharmacology at the University of Arizona, failed to win FDA approval for a clinical trial of marijuana for aids and cancer wasting. He believes the FDA turned him down because of political pressure. "If you want to study its harmful effects, you can get all the money you want," says Consroe. "But for this one, I would have spun my wheels forever." (An FDA spokeswoman declined to comment.)

It took Abrams five years, but he finally pushed his study through. A stubborn and irreverent oncologist who had watched hundreds of aids patients suffer brutal nausea, he won government approval in 1997 for the first clinical trial of marijuana in more than a decade. Marijuana proposals at the time required the approval of three agencies--the FDA, the Drug Enforcement Administration and the National Institute on Drug Abuse--and the DEA and NIDA had resisted. A DEA official worried in a letter about the political fallout if Abrams found positive results. "The government is saying there are no studies proving the medical benefits," Abrams fumed in 1996. "But they're also not letting studies be conducted."

Not true, says Steven Gust, special assistant to the director of NIDA, who has worked at the agency 15 years. "Ever since I've been here, there's been no prejudice against studying the medical applications of marijuana. Frankly, good proposals weren't coming in. The people you've talked to had a bad experience getting approval, and that's going to color their perception."

Whatever the case, Abrams and Gust agree that the government and medical-marijuana researchers are now working together. Abrams has two approved studies under way, and the State of California has founded a new, grander version of its old therapeutic research program. The Center for Medicinal Cannabis Research, which opened at the University of California two years ago with a yearly budget of \$3 million, currently supports 11 studies that have received federal approval.

To be sure, many scientists--especially in the government--still squirm at the very idea of medical-marijuana research. Despite encouraging anecdotal reports, the National Institutes of Health hasn't initiated a study of cannabis therapeutics in two decades, leaving California's young center as the only U.S. research institution doing the basic science. Marijuana remains the only drug that researchers must acquire directly from the feds. If the FDA and DEA approve, scientists can get even ecstasy from outside labs, but NIDA is the sole source for cannabis, requiring a third bureaucratic layer. "In an era of privatization, it's shocking that the government insists on a monopoly so that it can choose not to provide marijuana to projects it doesn't like," says Rick Doblin, founder of the Multidisciplinary Association for Psychedelic Studies, a nonprofit pharmaceutical firm. (For 18 months, Doblin's association and the University of Massachusetts Amherst have unsuccessfully sought a license to grow research-grade cannabis at the university.)

Not every country is as pot-phobic as the U.S. Scientists in Britain, which has effectively decriminalized personal use of small amounts of pot, have moved well beyond the preliminary work being done in the U.S. Britain's GW Pharmaceuticals plans to publish results of a large study of its new marijuana product, a whole-cannabis extract rendered into a mouth spray. That way, patients avoid the lung damage of smoking. The British government is likely to make the spray available for prescription if published results are as good as the company promises.

In this country, new drug products like GW's spray rarely appear without cordial cooperation among pharmaceutical companies, research institutions and government officials. Such partnership could take years to develop. But the politics has leaped well ahead of the science, meaning voters will decide long before physicians whether medical marijuana is an oxymoron.

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