ALASKA LEGISLATURE COMMITTEE FILES 1987-1988 8672
5248 SHES SB 32

MARIJUANA: THE MYTH OF HARMLESSNESS GOES UP IN SMOKE

New medical research puts a match to the myth that smoking marijuana is not harmful. The real dope is that the daily habit is damaging to the body as well as the mind.

by Peggy Mann

Is marijuana just the "innocent high" some have made it out to be? New medical research into the effects of this widespread drug points to heretofore unknown risks, as this exclusive two-part Post *series will show.*

"It's unreal," the school guidance counselor told me. "The kid looks you straight in the eye and says—full of conviction—'Well, pot doesn't hurt *me*!' His grades have slid from As and Bs to Cs and Ds. He's been put off the basketball team because of poor performance. He's irritable, hostile, always tired, feels depressed. He cares less about everything. He has a cough, chest pains. He's really going down the tubes. But blowing grass every day, he insists, has no relation to any of this.

"To my mind, the scariest thing about marijuana is that the user can't see what the drug is doing to him. Or, if he does admit to a symptom, he shrugs it off. Yesterday a seventh grader told me, 'I know pot's done bad things to my memory. But I don't really need my memory because I decided I'm not going to college.' "

The guidance counselor is Rick Gibson from Goddard, a small town in Kansas. I met him at lunch in another small Kansas town, Wellington. We were both attending a two-day "Grass Roots Conference on Grass." Wellington's population is 8,500. The school auditorium has 1,000 seats. And both days there was standing room only. Physicians, teachers, school administrators, guidance counselors, psychologists and parents came from all over Kansas and from nearby states to attend.

The Wellington conference was part of a burgeoning new movement throughout America. Schools and parents' groups are waking up to the fact that: (1) marijuana abuse has reached pandemic proportions among our youth; (2) something must be done about it; and (3) they are the ones who must do it. They realize that a vital first step is to educate themselves about the rising tide of medical evidence showing that pot can have serious psychological and physical effects. It can cause cellular damage and impair lung function, the reproductive system and the brain. Furthermore, the younger the user, the more deleterious the effects.

The roster of speakers at Wellington was an impressive one. The first speaker after lunch was Dr. Harold Voth, senior psychiatrist and psychoanalyst at the famed Menninger Foundation in Topeka, Kansas. He has studied the psychopathology of marijuana in depth for the past eight years. Coincidentally, his first point carried on from the one the guidance counselor had just made to me.

"Marijuana produces a wide spectrum of symptoms," said Dr. Voth. "Some affect some people; some affect others. And there are those who seem to 'get away with it' reasonably well, for a while. But there is one truly pernicious symptom—specifically related to marijuana—which seems to be evident in *every* chronic pot user, youngster or adult. This is the extraordinary refusal to accept the hard scientific evidence about the harmful effects of marijuana. The user will scoff at the evidence, twist it, pervert it, call it 'reefer madness'—anything except look it straight in the face.

"This may be one reason much of the media have, until recently, done shockingly little to relay the medical findings about the harmful effects of marijuana to the American public.

"In my opinion, marijuana use in the United States today constitutes a national crisis, and all-out efforts from all segments of our society are essential in view of the enormous harm being done to millions of Americans, particularly our youth."

Statistics on youth drug abuse clearly show why Dr. Voth's prescription for "all-out efforts" must be heeded on a national scale. For example:

- According to a report published by the House of Representatives Select Committee on Narcotics Abuse and Control, "The United States is the most pervasive drug-abusing nation in history and marijuana is our most pervasive illegal drug of abuse." Says Congressman Lester Wolff (D-NY), chairman of that committee: "Our young people are the first in all history to have used marijuana on a mass scale. Neither this nation—nor any other nation—has ever before faced a problem that is so insidious and so dangerous."
- Last year, according to the federal government's drug abuse network, marijuana accounted for the second largest number of admissions to our federally funded drug treatment facilities, and 33 percent of these had started their pot use before age 14.
- According to a recent national

drug abuse survey covering ages 12 and up (1976-1977), use of marijuana is twice as high for youngsters as for adults, and use by youngsters ages 12 to 17 increased by nearly a third in one year. (A new national survey has just been carried out by the National Institute on Drug Abuse and, according to Dr. Robert Peterson, assistant director of research, "We would be very surprised if this did not show an increase in use, especially among young users.")

- According to the High School Senior Survey, the only national drug abuse survey taken every year since 1975 (representing every state except Alaska and Hawaii):
  - In 1979, one out of ten high school seniors smoked pot daily, or almost daily—an 80 percent increase since 1975. Of these, daily users averaged 3½ joints (marijuana cigarettes) a day; 13 percent smoked more than seven joints daily.
  - Of the 50 percent of seniors who smoked pot at all during 1979, 37 percent said they "usually stay high three-to-six hours." (Add to this the fact that marijuana is up to ten times more potent than that smoked a decade ago.)
  - Forty-nine percent of all seniors who used pot "during the past 12 months" also used one or more additional illegal drugs during that period.

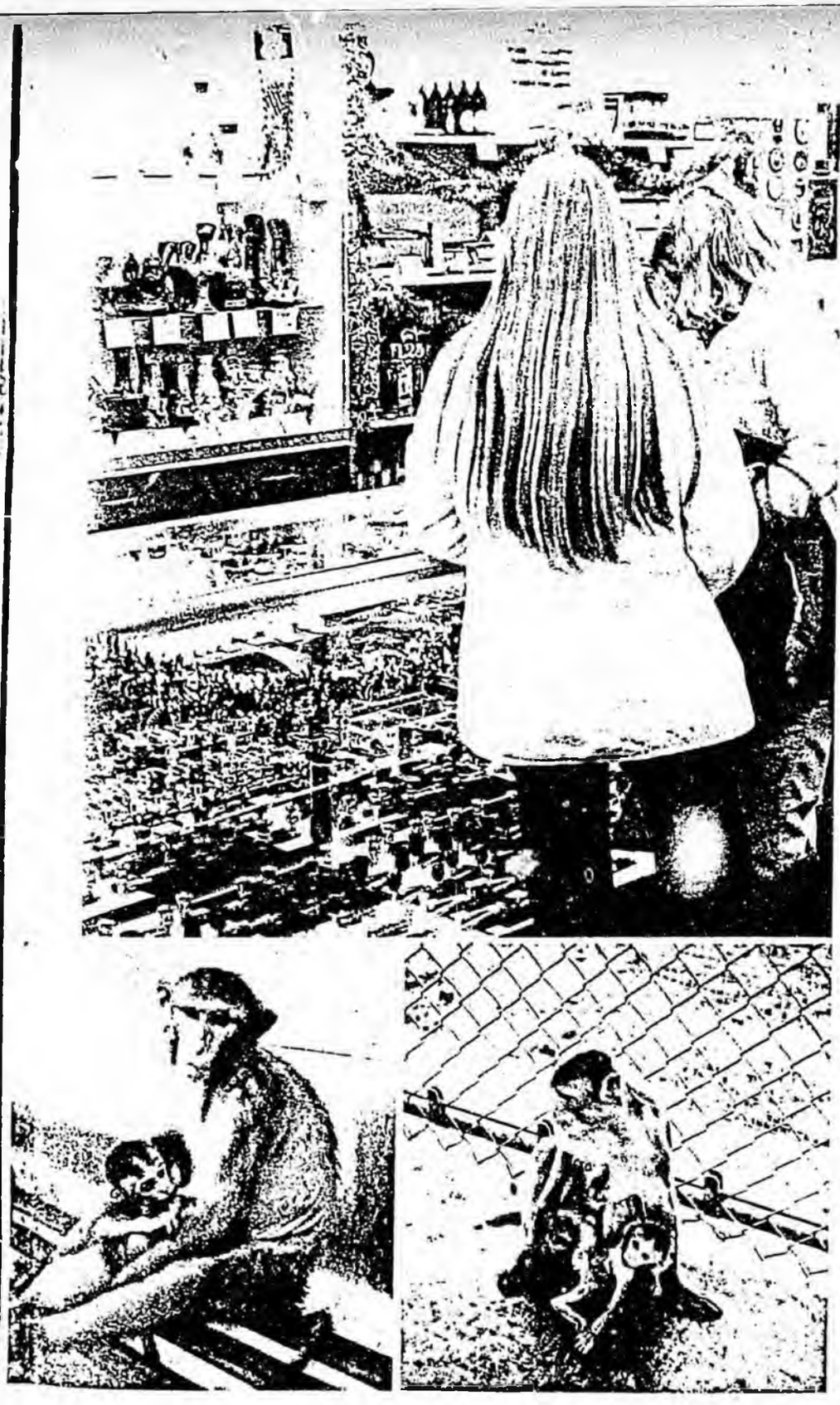
Popular drug-culture magazines teach how to grow your own, how to smuggle dope into the U.S., how to dress for pot parties, how to get around the law. Their advertisers reach a market of young people with money to spend, and the drug paraphernalia in their pages is available by mail—portable head shops, accessible to young residents of even the smallest, most remote communities. (Paraphernalia shops have been outlawed in Indiana.)

It is worth noting that this study surveys only those students who have made it to the end of their senior year. Drug use among dropouts is notably higher than among those who finish high school. (In some areas, for example, grocery store delivery boys no longer take coffee breaks, but "pot breaks.") Also not included are those who were not in school the day the survey was taken. Truancy is another "symptom" of regular pot use.

All recent state, city, suburban and rural surveys show that pot use has increased rapidly among youngsters of all income levels and all grade levels. with the highest increase at junior high school age. Throughout the country, surveys show that junior and senior high school kids are getting stoned on the way to school, during school, after school and at home—where they often "smoke out the window" or burn incense to cover the smell. One local newspaper series on the subject started: "For many middle school students, marijuana has replaced Wheaties as the morning 'meal.'"

In some areas, pot use starts as early as the fourth and fifth grade. If the saying is true, "as Maine goes, so goes the nation," it is worth noting that a 1979 two-county survey in rural Maine showed that in the fourth grade, 6 percent had tried marijuana at least once and one percent had used it "many times." ("And," says Mel Tremper of Maine's Office of Alcohol and Drug Abuse Prevention, "as drug use goes, we in Maine are kind of behind the times.")

California is a state "ahead of



Rhesus monkeys exposed to the human equivalency dose of one to two joints per day for three years exhibited a loss of drive, motivation and interest in the care of their offspring. A picture of a control, or non-drugged, rhesus shows a rhesus mother nicely nursing her baby. But the THC-treated mother (right) has been exposed to the human equivalency dose of one to three joints a day. Typically, these mothers didn't nurse their babies, groom them, retrieve them or cuddle them as the control mothers did. Dr. Ethel Sassenrath at the Primate Research Center of the University of California, who conducted the experiments, also noted that the THC-exposed babies showed deficits in attention and over-concentration on different stimuli in the environment—the types of deficits of behavior which indicate that the central nervous system had been affected in early development.

"The target for drug paraphernalia in the 1980s is ages 6 to 16," the operator of one of Florida's largest head shop chains recently admitted, claiming it was "an industry decision." Organized campaigns of this sort, added to tremendous peer pressure, are misleading young people into believing that pot smoking is a normal part of growing up.

the times" in this area. Dr. Richard Blum, one of the country's foremost authorities on drug abuse, studied 3,200 school children in California and found that some started pot use in third grade. Said Dr. Blum: "The phenomena that appear in California generally appear in the rest of the country several years later." Dr. Blum's survey was conducted in 1976.

For the past two years, pediatrician Dr. Ingrid Lantner has been speaking on the subject of marijuana at schools in the suburbs of Cleveland, Ohio. She speaks two or three times a week, often to fifth and sixth graders. She always asks them: "How old is the youngest child you know who has smoked marijuana?"

Dr. Lantner told me: "I have never asked this question without hearing about a two- or three-year-old who has been given marijuana by older siblings or parents—and not only once. I know several youngsters who have been smoking daily since they were six years old. In all these cases, the parents are users. I have never known of a grown-up who would give a child that age a tobacco cigarette or any other drug."

Dr. Lantner also asks for written questions from her young audiences. Every time she speaks she receives one or two questions which indicate that parents give pot to their young children. Two typical questions:

"I am ten. My parents let me smoke pot since I was six. Will my eggs be damaged?"

"My brother smoked M.J. since age seven but not every day. Will he have his growth affected? He is now 11. He gets the M.J. from my mother."

Another question Dr. Lantner often receives from fifth and sixth graders is: "What shall I do if someone physically forces me to

smoke pot?"

"School principals tell me," says Dr. Lantner, "that after a ball game, a group of potheads—older students—often come around to sell drugs, and they're very aggressive with the little ones, insisting they buy and smoke on the spot. This happens in a nice, upper-middle-class area in the suburbs of Cleveland."

Nor are the suburbs of Cleveland, Ohio, the only area in the country where parents are giving pot to very young children. Take Missouri, for example. Ed Moses, drug information officer of the state of Missouri, works full time lecturing and teaching about drug abuse. "Every year drug abuse is affecting younger age groups," he told me. "They commonly start feeling the pressure to turn on as early as the fifth and sixth grades. Also, every year the marijuana is getting stronger and more easily available in larger quantities.

"I think the most disturbing thing I've found is many parents' attitude that marijuana is so harmless that it's okay to reward their three- and four-year-old child with getting high.

"For example, at parties, the parent will let the three- to five-year-old child carry the joint around to the toking [pot-smoking] guests. And, as a reward, the child is allowed 'to take a hit' and get stoned. This is becoming more and more common among young parents who are heavy users.

"The youngest I have seen in a home was with a couple in their early 20s who got their nine-month-old baby high by 'shotgunning' the child [turning the cigarette backwards with the lit part in the mouth so that a concentrated rush of smoke can be blown into someone else's mouth or face]. The father told me, 'We like to get Annie high so she won't be afraid to walk.' I pointed out that she was so stoned she couldn't even crawl. The father said, 'Well, that's cool. At least she's not afraid to try.' 'She boogies around when she gets high,' the mother said, laughing. This meant that the baby bounced around a little while. Then she sat—spaced out."

A kindergarten teacher in a South Texas town told me, "My

THC-Injected Mice Produce Abnormal Eggs

Current research indicates that THC (the active agent in marijuan may induce genetic mutation. One recent experiment involved mou ova (female reproduction cells; commonly called "eggs"). Two grou of 26-day-old female mice were used in the experiment. The contr group was allowed to proceed with a normal routine while the te group was injected with daily doses of THC. The animals were th allowed to mate with non-treated young adult mice. Forty-eight hou after mating, the animals were sacrificed and the fertilized eggs we recovered from the oviducts. Abnormal cells occurred in 37.5 perce of ova recovered from the THC-treated mice, compared with 10 pe cent in those obtained from the controls.

A normal ovum (left) shows the chromatin (that part of the cell nucleus that is composed of DNA and is the carrier of the genes) to be finely granular and evenly dispersed throughout and responsive to fertilization and normal cell division.

In stark contrast is the abnormal ovum (above), taken from the THC-treated mice, where the chromatin has clumped together. The fact that it has coagulated is an indication that it is damaged and probably is a nonviable chronosomal substance, in which case there would be no pregnancy at all.

A normal fertilized ovum demonstrates predictable cell division.

Irregular shapes and sizes of fertilized cells appear in the mice ovum the THC-treated group 48 hours after mating.

It was the conclusion of this research that THC does act as a mitotic (dividing cell) poison and therefore is considered a chromosomal mutagen. It is also important to note that unlike male sperm, which is replenished during the entire life of the male, the number of female eggs is determined at birth and, once they are damaged or destroyed, they can never be replaced—the damage is permanent.

children don't smoke pot. But the first grade teachers tell me that some of *their* children come in stoned—always the ones with older brothers and sisters."

Maryland is so "typical" that it is often referred to as "America in miniature." Certainly the 1978 Maryland statewide survey reflects what is being found in local surveys throughout the country: "Students began using one or more illegal drugs at about one year earlier than the same grade level use in the last Maryland survey (1975)." And the "one" drug is invariably marijuana. Most local surveys show that, each year, initial marijuana use drops one year lower.

Older siblings are the chief source of supply for very young users. Because the myth of marijuana's "harmlessness" has so permeated our society, youngsters often feel they are doing their smaller brothers and sisters a favor by getting them high. There is also another motive. If the younger child gets involved, he or she won't "narc" (tell Mom and Dad).

It is quite possible for Mom and Dad to be unaware of the fact that their children are stoned. With marijuana use it's easy to "hide the high" or to "come down" by dinner time. The clearest tell-tale symptom—red eyes—is handled by kids via eye drops. (The eye drop industry reports a boom in sales.) Youngsters who use a local swimming pool have an easy excuse—"chlorine in the water"—even though the closest they may have been to the water was hanging out in the locker room blowing grass.

There are, of course, discernable symptoms of the youngster who is a heavy pot user. Unfortunately, most of them are so much like the "blow up" symptoms of normal adolescence that many parents tend to disregard such as merely something their child will "grow out of." But this is not likely to happen unless the child gets some firm, supportive help from parents and from the school.

Parents should realize that even the "straight" kids (non-drug users)—who represent about 50 percent of most surveys of junior high and high school classes—are under constant peer pressure to "Try it: It's great." And this pressure to start pot use comes not only from peers. All kids are affected by aspects of adult industries which make drug use in general—and pot use in particular—seem like a normal part of growing up in America today.

For example, a recent survey in Atlanta, Georgia, showed that while one third of non-drug-using kids listen to rock music on the radio three hours or more a day, virtually *all* drug-using youngsters listen three or more hours a day. Some reported: "I listen all the time when I'm home." In addition, they have favorite records and cassettes that they put on when they're high and "float with them."

The same Atlanta researcher, Dr. Fred Crawford, studied the contents of rock lyrics to determine what messages they contained suggesting or supporting drug use. He found that more than half of the current rock songs had messages condoning or suggesting the use of drugs, and that many students start listening to rock music at about the time of first use.

And what do they hear when they listen? There are countless songs with "do drug" messages such as this from Eric Clapton:

Cocaine, cocaine
She's all right.

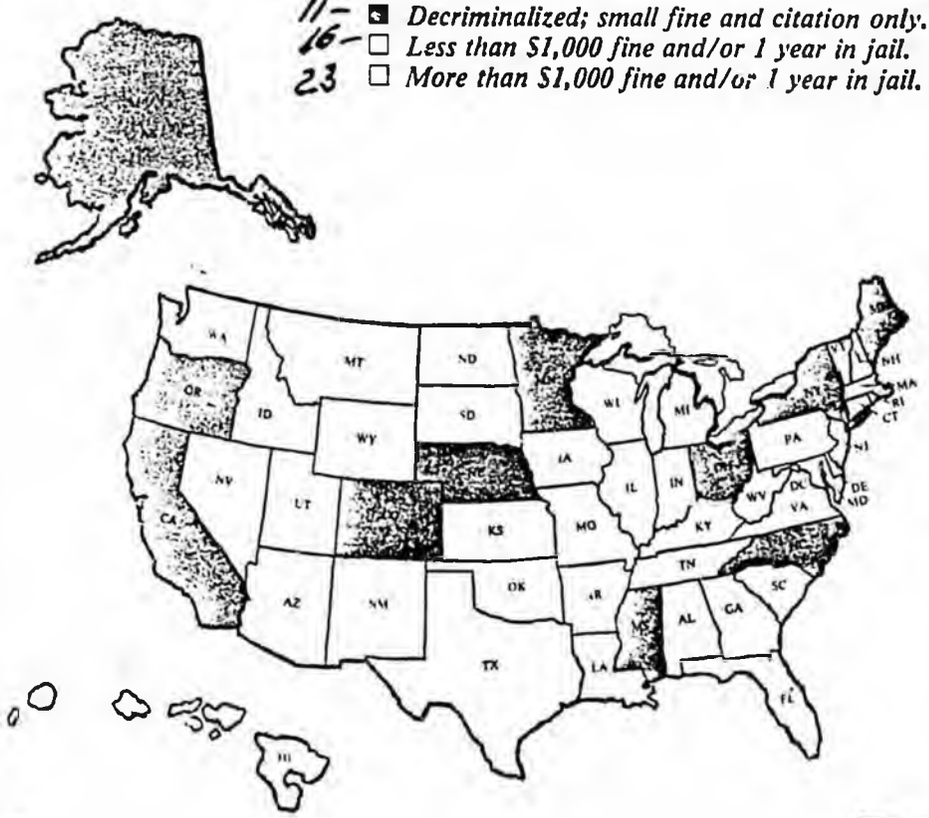
And this from Dr. Hook's Medicine Show the *Sloppy Seconds* album ("killer weed" is marijuana):

Some men need some killer weed
And some men need cocaine
And some men need some cactus juice
To purify their brains.
Blow your whistle,
Bang your gong,
Roll up something to take along
Feels so good it must be wrong
Freakin' at the freakers' ball.

Another example of the "mes-

First-time marijuana-possession penalities for 1 ounce or less:

11– ■ *Decriminalized; small fine and citation only.*
16– □ *Less than $1,000 fine and/or 1 year in jail.*
23 □ *More than $1,000 fine and/or 1 year in jail.*



In most areas, laws for possession of an ounce or less of marijuana (30 to 60 joints) for personal use are not enforced. Some say this is reason to relax the laws (decriminalization) or to eliminate them (legalization). However, in states which have decriminalized pot, law enforcement officials point out that marijuana use among youths has escalated greatly, and traffic accidents and drug-related crimes have increased dramatically.

sages" youngsters receive from the adult community comes from the drug paraphernalia industry—now a $3 billion business. A highly profitable line is the "kiddie" drug paraphernalia, which includes such items as baby bottles and "Catch-a-Buzz" flying discs which double as pot-smoking devices, skateboards and kiddie belt buckles for "hiding your stash" (your supply of pot), comic books which show how to cut and snort cocaine and *McGrussey's Reader*, an easy-to-read, 20-page primer which includes clear directions on how to roll a joint, a pot vocabulary, advice on what to wear to your first pot party, plus a packet of alfalfa "practice grass." For more advanced readers there is *The Whole Drug Manufacturers' Catalog*, one-third of which is devoted to "Kitchen Chemistry and Bathtub Dope: How to Produce Drugs from Non-Prescription Items and Household Chemicals in Your Kitchen Without Prior Chemical Knowledge."

In most states such items are legal and can be found in various varieties of stores, including posh gift shops, boutiques, record stores, flower shops and stores which specialize in magic, Oriental gifts, leather goods, smoking goods, etc., as well as in the "head shops." And some head shops advertise openly in school newspapers as "novelty shops." The kids know what they are, but (presumably) the teachers don't. One of the biggest head shop chain operators in Florida recently told Florida state legislator Mary Ellen Hawkins: "The target for drug paraphenalia in the 1980s is ages 6 to 16." He said this was an industry decision.

A. Non-marijuana smokers have more white cells with 46 chromosomes.

B. Marijuana smokers have an increased percentage of cells with fewer chromosomes.

While a normal cell has the typical complement of 46 chromosomes within its nucleus (left), recent experiments indicate that heavy-marijuana smokers have marked increases in the number of cells with micronuclei (nuclei with less than 46 chromosomes, as pictured right). The experiments were performed to determine the effects of marijuana on human lymphocytes (white blood cells, which are a major part of our bodies' defense systems). Five volunteers with histories of chronic marijuana smoking were used. They ranged in age from 22 to 32 and had histories of smoking at least ten marijuana cigarettes per week for six years or more. Seven healthy students who had no history of smoking marijuana served as the control group. After repeated periods of smoking followed by deprivation, blood samples were obtained from all subjects in the test group. Similar samples were obtained from control subjects on the same day. The cells from the non-marijuana smokers showed a 15 percent incidence of micronuclei, while the cells from the marijuana smokers showed a 36 percent incidence of micronuclei. Dr. Akira Miroshima of Columbia University noted that the marijuana smoker might run a greater risk of disease, since THC lowers our resistance to infection.

What does all this mean in terms of our youngsters' health? And what can parents look for as possible signs or symptoms of chronic pot use among youngsters?

The psychological symptoms are often the first to manifest themselves. These include decreasing school performance; increased irritability ("stop *hassling* me" flared out for no justifiable reason); a general apathy; depression; drastic, inexplicable mood changes; feelings of isolation; a cutting off of communication between parent and child and a general loss of interest in everything except pot smoking and the accompanying "kiddie drug culture."

There are two very common physical symptoms: a chronic cough—a bothersome, constant hacking—and chest pains. Says Dr. Ingrid Lantner, "I have yet to see a teen-age tobacco smoker complain of chest pains, but it's quite common among pot smokers. School nurses tell me this, too."

However, it is the nonvisible physical symptoms which may be the most damaging. And this is the information which is finally crossing the chasm between the scientific community on one shore, which has been putting forth these findings at ever-increasing rates, and the general public on the other shore. For years this chasm has not remained empty. It has been industriously filled with misinformation, distortion and perversion of the facts and, at times, even outright lies emanating from pro-pot organizations and individuals whose purpose seems to be to discredit the findings which prove that pot is harmful and to make it seem an essential and harmless ingredient of the "now" way of life.

Because of this constant surge of misinformation, which is still heard loud and clear throughout the land, pot smokers often have pat answers when confronted with the warning signals now coming loudly and clearly from the scientific community.

One common "turnoff" of these findings is the shoulder-shrug comment, "For every study showing that pot is harmful, there's another showing it's harmless."

This is simply not true.

One of the world's most knowl-

edgeable experts in the field of marijuana is Dr. Carlton Turner, director of the Federal Marijuana Project funded by the National Institute on Drug Abuse (NIDA). Dr. Turner and his associate, Dr. Coy Waller, have just completed a hefty two-volume work: *Marijuana: An Annotated Bibliography*. The first volume has already been published by Macmillan; the second will be published this summer. In preparing these works, Dr. Turner abstracted more than 5,000 scientific publications on cannabis (the plant from which marijuana, hashish and hash oil are prepared). He says: "As a scientist, I have to be objective. I am not a crusader for or against any drug. I am for evaluating any drug on its merit, which I base on all scientific publications about that drug. There is not a single paper on the crude drug marijuana which gives it a clean bill of health, not a single paper to support it as an innocuous drug.

"A widely quoted study of 30 Jamaican cane workers was never published by a scientific journal. It could not stand the scientific review process.

"There *are* some reports on *individual* cannabinoids indicating possible therapeutic use." (Cannabis contains 61 known cannabinoids—substances unique in nature, found only in the cannabis plant.) "However, it must be remembered that any drug has some side effects, and with the broad biological action of the cannabinoids at the cellular level, the side effects may outweigh the benefits in long-term use. This is the reason that marijuana has no place in modern medicine. Using marijuana would be like giving people molded bread to eat to get penicillin.

"Media, with some exceptions, have not taken the time to understand the nature of the crude drug marijuana. If you attend a conference and there are 15 scientific papers cautioning against the use of marijuana, and *one* saying that a single extracted cannabinoid might be useful in a therapeutic area, the media headline this by saying that *marijuana* has been found to be useful. The findings are reported in such a way that the public is led to believe joints of street pot are being smoked by people with glaucoma or by cancer patients to control nausea after chemotherapy treatments, when the research is actually being done with a synthesized THC capsule. And by the time this 'news' sifts down to the school yard, you have kids saying that pot cures cancer, pot cures nearsightedness and pot cleans out your lungs after you smoke tobacco cigarettes." (The latter comes from early findings which indicated that marijuana might be helpful in cases of asthma. Further research clearly showed just the opposite is true.)

"Incidentally, why the media have generally been so 'up' about publicizing the possible medical benefits of marijuana and so 'down' on relaying the consistently emerging evidence concerning the harmful effects of marijuana is a matter to be comtemplated."

Another common argument of pot-smoking youngsters is this: "You have your martini, so why can't I have my pot?"

Dr. Nicholas Pace has a solid answer for this question, and he is well qualified to give it. Dr. Pace is the co-founder and past president of the New York City Affiliate of the National Council on Alcoholism. He is also one of the founding directors of the American Council on Marijuana and Other Psychoactive Drugs.

Dr. Pace points out: "There are two important differences between alcohol and marijuana. First, alcohol has a single chemical, and it is water soluble. One ounce is metabolized and is completely excreted from the body within 12 hours.

"What about pot? Youngsters like to consider it a 'natural weed.' Some even believe it to have health-giving properties. In reality, however, cannabis is an extremely complex crude drug containing 421 known chemicals. When you smoke a joint you are combusting these chemicals into hundreds of other different compounds. And we don't know how they are affecting the body.

"We do know, however, that among the 420 basic chemicals are

The only long-term (20-year) study of the effects of THC on the male reproductive cell (sperm) was conducted in the small laboring village of Piraeus, Greece, by Dr. Marietta Issidorides and Dr. Costas Stefanis of the University of Athens, Greece. Spermatozoa from nonsmokers and from chronic hashish smokers (hashish has a high concentration of THC) were photomicrographed. Normal spermatozoa from a non-hashish-smoking male show a proper density, indicating that it is rich in protein and other essential chemical substances. In the center and right panels, sperm taken from a hashish-smoking male shows a definite breakdown of protein substances and a clumping together of chromosomal material. The research team also noted changes in the ultrastructure of the spermatozoa of chronic hashish-smoking males which could result in genetic disturbances or prevent fertilization.

61 known cannabinoids (new ones are being discovered all the time), and so far scientists have studied only a few of them. We know that at least four of the cannabinoids are psychoactive, or mind-altering. But a few of the nonpsychoactive cannabinoids which have been studied thus far appear to be even more harmful to certain organ systems than the psychoactive ones.

"Therefore," says Dr. Pace, "the first important point to be kept in mind is that even the so-called 'NIDA marijuana' used by scientists is, in fact, a Pandora's box of unknowns."

"NIDA marijuana" is grown on a well-guarded five-acre "pot farm" on the outskirts of the University of Mississippi. This project, funded by the National Institute on Drug Abuse and directed by Dr. Carlton Turner, supplies to researchers marijuana which has a relatively stable Delta-9-THC content of about 2 percent. (This is the chief psychoactive cannabinoid in marijuana.)

Dr. Pace points out that so-called "good street pot" has a four, five or even six percent THC content. Therefore, sobering as the research findings are, they gain an even greater impact when we realize that they represent work with THC half as potent as that which many of our youngsters are smoking regularly today.

"The second important point regarding marijuana," says Dr. Pace, "is the fact that it is fat soluble, like DDT. And we have, of course, banned the use of DDT because it accumulates in body cells and organs.

"The cannabinoids are not only fat soluble. They are, in fact, lipophilic—fat loving. The fatty sections of cells and membranes and the fatty organs of the body act like magnets attracting the cannabinoids. The cell membrane—the coating surrounding the cell—is at least 60 percent fat. When the fat-soluble cannabinoids dissolve in the cell membrane, they make it difficult for the most important constituents of the cell, the proteins, to enter. And cannabinoid clogging of the cell has additional deleterious effects.

"What about the fatty *organs*? It should be remembered that the chief fatty organs of the body are the gonads (sex glands) and the brain. Indeed, the three-pound human brain is composed chiefly of fat. As one prominent researcher once noted: 'We're all fatheads, from that point of view.' "

Dr. Pace and every other marijuana researcher I have interviewed agree that the fat solubility of marijuana is the most important—and ominous—single factor about this drug.

Why? Dr. Pace puts it this way: "The most studied cannabinoid, the popular 'Delta-9,' has been traced radioactively in the body in human and animal studies. All the studies show that it takes three days to a week for the body to rid itself of *half* the THC in a single joint and much longer (some studies show up to 30 days) to get rid of all of it. This means that even if a youngster smokes only one joint a weekend, about half the THC and other cannabinoids *remain* in the body. Half the cannabinoids in next Saturday night's joint are added to the first. And so on, for a smoke-filled series of Saturday nights."

Dr. Robert C. Gilkeson, who has spent 15 years in neurophysiologic research, puts it this way: "No drug or chemical improves the normal cell. Marijuana is a known intoxicant. Toxic means poison. Anyone who smokes or ingests more than the equivalent of one marijuana cigarette every 30 days will accumulate an acute neurotoxic substance in his or her body."

What are the results of "cannabinoid accumulation?"

A single article can only touch the iceberg's tip. This becomes clear when picking up a 777-page volume, *Marijuana: Biological Effects*, published by Pergamon Press. This contains 50 scientific papers given at the two-day Reims Conference held in France in July 1978. The conference was limited to marijuana's effects on four areas: the lungs, the reproductive system, the brain and the cells.

The September issue of the *Post* will discuss these four areas in depth, as well as give some useful pointers for parents and other interested adults who wish to combat this "grass fire" of marijuana use among our young people. ★

PUTTING A MATCH TO THE MARIJUANA MYTH

Most kids are fully convinced that the use of marijuana is not harmful. But new medical research proves them dead wrong.

by Peggy Mann

We have found that students in the lower grades will look their counselors straight in the eye and say—with full conviction—"Pot doesn't hurt me!" But the latest medical research has determined that marijuana can cause cellular damage and impair lung function, the reproductive system and the brain. In the conclusion of this article, we take a closer look at these four areas of abuse—and offer suggestions to parents and other adults interested in combating this "grass fire" now raging through our schools.

Although one in every ten high school seniors admits smoking pot daily, and in some areas pot usage now starts as early as the 4th and 5th grades, the highest usage of all is in the 18- to 25-year age group.

Marijuana and Cellular Damage

Many scientists, including pioneer "pot researcher" Dr. Gabriel Nahas, consider the reports on marijuana's impairing effects on body cells to be the most alarming because, as Dr. Nahas says, "they are the underlying cause of all the other deleterious effects that have been reported."

Not only do cannabinoids clog the cells, inhibiting their functions to some degree, but many studies have shown that heavy pot smokers have an abnormally large number of abnormal cells.

Dr. Akira Morishima, of the Columbia University College of Physicians and Surgeons, has done studies on the increased incidence of cells in marijuana smokers which have less than the normal number of chromosomes and which tend to revert back to the normal level after the individual has stopped smoking pot. In more recent studies, published in June 1980, Dr. Morishima found that THC disturbs the *movement* of chromosomes which, he says, "probably accounts for the production of cells with an abnormal number of chromosomes." A similar finding has just been published by Dr. Arthur Zimmerman in Canada, using an entirely different methodological technique.

Pot advocates are swift to "discredit" chromosome studies by saying that "aspirin and coffee also cause chromosome breaks." Dr. Morishima points out that his studies did not relate to chromosome *breaks*. Furthermore, in the 1980 studies he used the same technique to test the effects of aspirin, caffeine and alcohol on chromosome movement. He also used "comparable doses," except that in the case of alcohol, "we went up to 100 times the equivalency dose." The result? Neither aspirin, caffeine nor alcohol produced abnormal movement of the chromosomes.

As early as 1973, Dr. Nahas found that THC lowered the rate of cell division by diminishing the cell's ability to make DNA, RNA and essential proteins. DNA is the all-important genetic material of the cell. RNA controls gene "expression." These findings have since been replicated by scientists in 12 important research centers in the U.S. and abroad.

Said Dr. Nahas: "These findings indicate that the pot smoker may not only be damaging his own mind and body, but may be playing genetic roulette with his or her unborn children."

Marijuana, Sex and Reproduction

There are other ways in which pot smokers may be damaging their unborn children.

As noted, cannabinoids collect in the fatty gonads *and* in the brain. In the brain, THC seems to affect the hypothalamus which, in turn, affects the pituitary, a pea-like structure at the base of the brain which is a control center for sex and reproductive hormones.

It is not surprising that this double-barreled influence on the reproductive system should result in some dysfunction and abnormalities.

A sexual performance study of 500 pot-smoking men was made by Dr. Robert Kolodny of the Reproductive Biology Research Foundation in St. Louis. He summed up: "The general trend was that with increasing use,

there were lower rates of sexual activity and a lower frequency of orgasm." A study of 1,238 male users in India showed similar results.

Other researchers have shown that marijuana smoked in moderate to heavy doses results in an abnormally large number of abnormal sperm. And this is dose-related. The more joints smoked, the more abnormal sperm there are.

Dr. Carol Grace Smith did a recent study on male rhesus monkeys. Both males and females of this breed have a reproductive system close to humans. "In fact," says Dr. Smith, "under the microscope, rhesus sperm are almost indistinguishable from human sperm." She gave male monkeys the "rhesus THC equivalent" of one to two joints a day. She summed up: "THC profoundly inhibits testosterone and hormones which stimulate the sex organs, bringing them down to the level of a castrated animal. One dose 'shuts down production' for as long as 24 hours."

Testosterone is the all-important male sex hormone. A number of other human and animal studies have also shown that THC lowers the testosterone level in males.

There has been only one study made on long-term (20-year) human male cannabis smokers. The researcher, Dr. Mariette Issidorides, of Greece, summed up: "Cannabis interfered with protein substances essential for the normal development of the sperm, and it altered the metabolism of the sperm cell, thus possibly affecting expression of the genetic material."

Since males produce so many millions of sperm, all indications are that, if the pot smoker ceases and desists, sperm return to normal. Females, however, may be another matter. An infant girl is born with her lifetime supply of eggs. If these are damaged, there's no replacement. And cannabinoids collect in the ovaries, a fact proved by radioactively tagged THC. What effect might this have on the eggs? Thus far, the only researcher to have delved into this question is Dr. Akira Morishima. He worked with "teen-aged" female mice. He gave them miniscule mouse-size doses of THC. Scientists figure in "human equivalency doses," which can be "checked out" by testing THC in blood levels. If a mouse has a percent of THC in its blood which is equal to the percent of THC a human adult has in his or her blood after smoking—for example, one joint at 2 percent THC—then this is the "human equivalency dose." According to human equivalency charts just published by another "pioneer pot researcher," Dr. Harris Rosenkrantz, Dr. Morishima's female mice received the THC "equivalent" of an adult woman smoking two joints a day. In his report, published in July 1979, he revealed that in the control group, very few of the mice had abnormal eggs. But in the THC-exposed group, about half the eggs were dying or had died. "And," said Dr. Morishima, "of those that lived, 20

Magazines extolling the joys of drug taking are found on newsstands throughout the U.S. As some fold, others are born. The slick High Times *boasts 4 million readers. Such publications make illicit drugs seem as "normal" as popcorn and apple pie.*

...30 percent looked unhealthy."

Dr. Ethel Sassenrath at the Primate Research ...ter of the University of California has done other ...es of investigation into pot's effects on the female ...productive system. She works with female rhesus ...keys, whose reproductive system is very close to ...human female's, including a 28-day menstrual cy... Every day for three years—she even came in on ...ristmas—Dr. Sassenrath fed her monkeys the THC ...man equivalency dose of one to two joints. (She gave ...m on raisin cookies.)

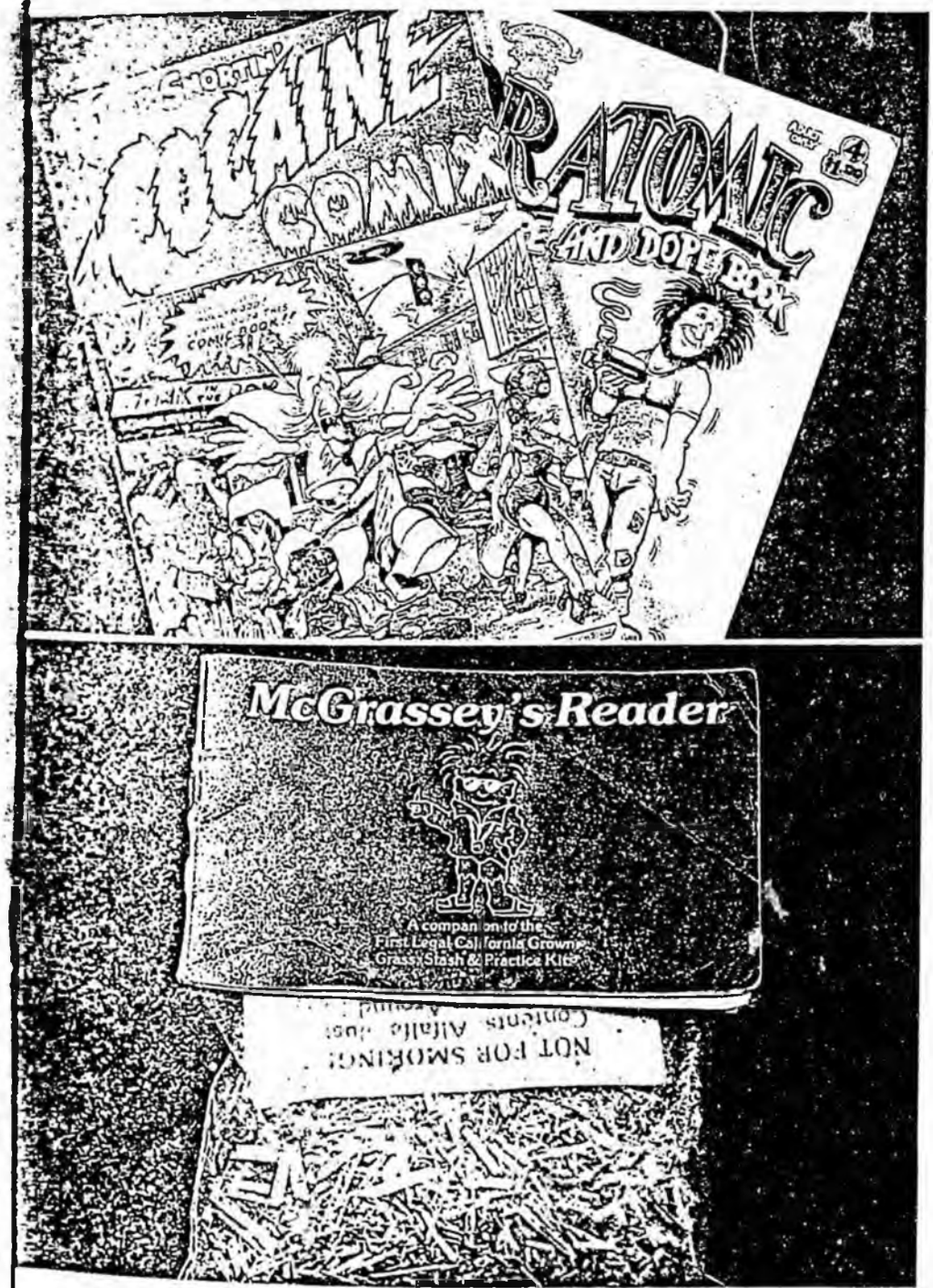
Result: Forty-four percent of the pregnancies of the THC-treated mothers did not result in living offspring. The losses occurred as abortions, reabsorptions, *in utero* death, stillbirth or death just after birth. The control mothers had a 12 percent birth loss—which is normal for a monkey colony.

Of even greater concern were the results obtained when the pathologist did microscopic evaluations of tissues and organs from the dead fetuses and infants. This was a double blind study. He did not know whether tissues came from the THC-exposed offspring or the offspring of undrugged mothers. Result: Although the dead THC-exposed offspring appeared to be normal, in each case he found subtle developmental abnormalities in various organ systems and tissues which were not found in the offspring of the undrugged mothers.

"Furthermore," said Dr. Sassenrath, "the THC-exposed babies that survived acted differently than the others. They over-responded. They didn't seem to have normal 'brakes' on such behavior as active playing without stopping or clasping cagemates who struggled to get away. They all showed deficits in attention and over-concentration on different stimuli in the environment. They had the type of deficits in behavior which indicate that the central nervous system has been affected. This kind of subtle behavioral difference can be characteristic of marginal brain damage in early development."

It has been well established that THC easily passes through the placenta. But how does it affect the placenta itself? In March 1979, Dr. Paige Besch of Baylor College of Medicine in Houston, Texas, completed a four-year study on the subject. He found that the more THC was added to the human placenta, the less estrogen was produced. Says Dr. Besch: "Decreased estrogen results in decreased blood flow to the placenta, which means decreased nutrition to the developing baby."

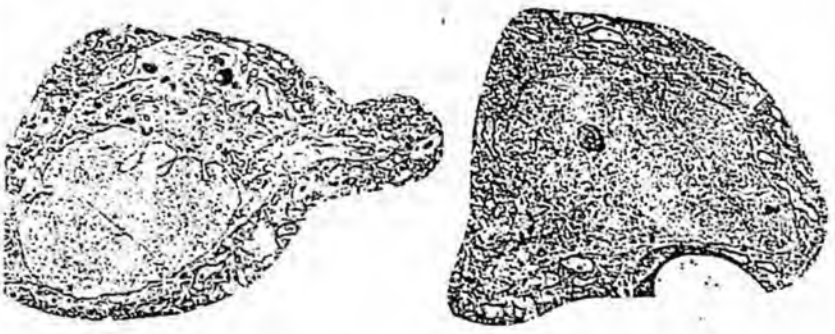
Other scientists working with rhesus monkeys and with human females have found that THC appears to interfere with the hormonal system and with the menstrual cycle. For example, Dr. Joan Bauman and Dr. Robert Kolodny found that 38.8 percent of pot smokers they studied had defective



A profitable branch of the drug publications industry is aimed at children. Comic books show how to "smoke dope," how to cut and snort cocaine. McGrassey's Reader, an easy-to-read primer, explains how to roll a joint and comes with "practice grass" (alfalfa), rolling papers and a "roach clip."

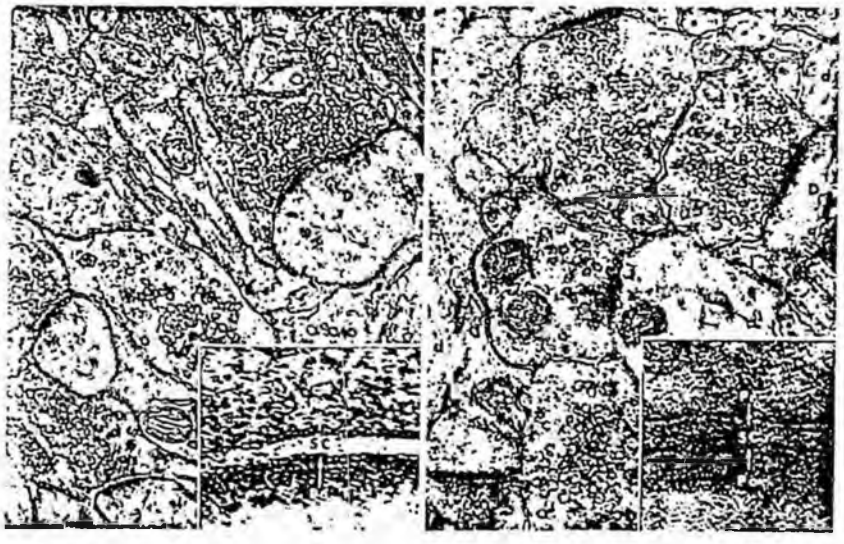
Marijuana and Brain Damage

To determine the effects of marijuana on the brain, Dr. Robert Heath of Tulane University gave rhesus monkeys 2 to 3 "monkey-sized" joints per day (inducing blood levels equal to those of human subjects smoking 3 joints per day) for six months. A control group was given an equal number of marijuana cigarettes with the active ingredient THC removed. Heath reported significant damage.



Normal Brain Cell *Damaged Brain Cell*

While no changes were noted in cells taken from the "control" group, cells from the THC-exposed brains show a marked increase in the number of inclusion bodies that appear in the nuclei, and the rough endoplasmic reticulum is disrupted. These changes in the cell structure may be interpreted as a sign of injury in most cells, including brain cells. These injured cells have a reduced capacity for normal function.



Normal Synapse *Damaged Synapse*

Vital to survival, the synaptic membrane serves as the body's communications network, transmitting messages to the brain. While a normal synapse (left) allows for free flow of messages, the THC-exposed synapse (with widening of the synaptic cleft, electron opaque materials in the cleft and some clumping in the synaptic vesicle) will not properly transmit these necessary messages.

In the light of recent experiments, little doubt can remain as to the gradual, yet significant, consequences of smoking marijuana. Perception, motor activity, sensation, emotional response, motivation, memory and states of awareness can all be affected.

menstrual cycles, compared to 12 percent of the non-pot smokers. Sex hormones were also affected.

Dr. Bauman pointed out: "Researchers are forbidden by FDA regulations to administer marijuana to teen-agers in the course of controlled experiments. But we are particularly worried about what the drug may be doing to pre-teen and teen-aged girls. Any of the effects we found could be even stronger before the body's endocrine-regulated systems have matured."

It should also be remembered that in our country, for the first time in the history of any country, pre-teen and teen-aged girls are smoking cannabis on a mass scale. Our pot-smoking teen-aged girls, therefore, are unwittingly turning themselves into guinea pigs.

Many animal experiments have shown that the mother's THC exposure affects the "next generation," to whom no additional THC has been given. One particularly strange result was found by Dr. Susan Dalterio of the University of Texas Medical School at San Antonio. She gave nursing mice mothers a tiny drop of sesame oil containing THC—the human equivalent of two joints a day. Aside from one equally small dose the day before they gave birth, none of the mother mice had ever before received any THC. The offspring were fed no THC at all. Yet when the males reached young adulthood, they all became very fat and half were "grossly overweight": 50 grams. (The normal male mice of their breed weigh 10 grams.) These fat fellows were also sexually inept, "showing," said Dr. Dalterio primly, "deficient copulatory behavior." When autopsies were performed, there were globs of fat throughout the bodies of all the male mice—whose only exposure to the drug had been as infants, through their mothers' milk.

Other researchers working with mice, rats, dogs, rabbits and rhesus monkeys have shown that the mother's exposure to THC—or to other cannabinoids—causes smaller-than-normal litters and smaller-than-normal babies.

Research on animals has proven that marijuana is not teratogenic

[producing deformed babies]. It is, however, embryocidal [having a fetus-killing effect].

Marijuana and the Brain

Pot is smoked to get a "high"—to "alter" the mind. But no smoker wants his brain cells affected, structurally changed. Yet this may be what is happening.

Dr. Robert Heath, chairman of the department of neurology and psychiatry of Tulane University, has pioneered in the study of the limbic area of the brain, working with humans and with rhesus monkeys. This particular brain area is very similar in both species. This so-called "old mammalian brain" is the site of such specifics as time sense, sexual activity, appetite and emotions—both pleasurable and painful.

In July 1978, Heath showed some startling slides to more than 100 marijuana researchers at the Reims Conference. These were magnified pictures of brain cells from rhesus monkeys that had been exposed to the smoke of two to three "monkey-sized" joints a day (one-fourth the size of an average human joint) at 3 percent THC for six months. The monkeys had received *no* THC for the following six months (equivalent to a much longer time in human terms). Then they were sacrificed and the pictures taken.

Dr. Heath, a distinguished-looking, white-haired man, stood by the large screen. Using a pointer, he illustrated what were, perhaps, the most sobering slides shown during the entire two-day conference. He identified the following structural brain cell changes which were glaringly evident when the cells of the THC-exposed monkeys were compared to the cells taken from the same brain area of the control monkeys.

"Here," said Dr. Heath, "we see an accumulation of granular material in—and a definite widening of—the synaptic cleft between nerve cells [where the flow of messages jumps from one cell to the next]. This," he said, "causes a slowing down in the movement of the messages and may impair some brain processes."

The pointer moved on to another spot. "Here we see a clumping of the synaptic vesicles [small sacs in the endings of nerve cells, containing the essential nerve transmitters: chemical activators of the brain]. We find the identical conditions in cases of early brain damage in humans.

"And here," said Dr. Heath, "note the significant increase in inclusion bodies. These foreign substances are seen in degenerating brain cells of very old animals and humans, but not to the degree that we see them here in very young pot-exposed rhesus monkeys."

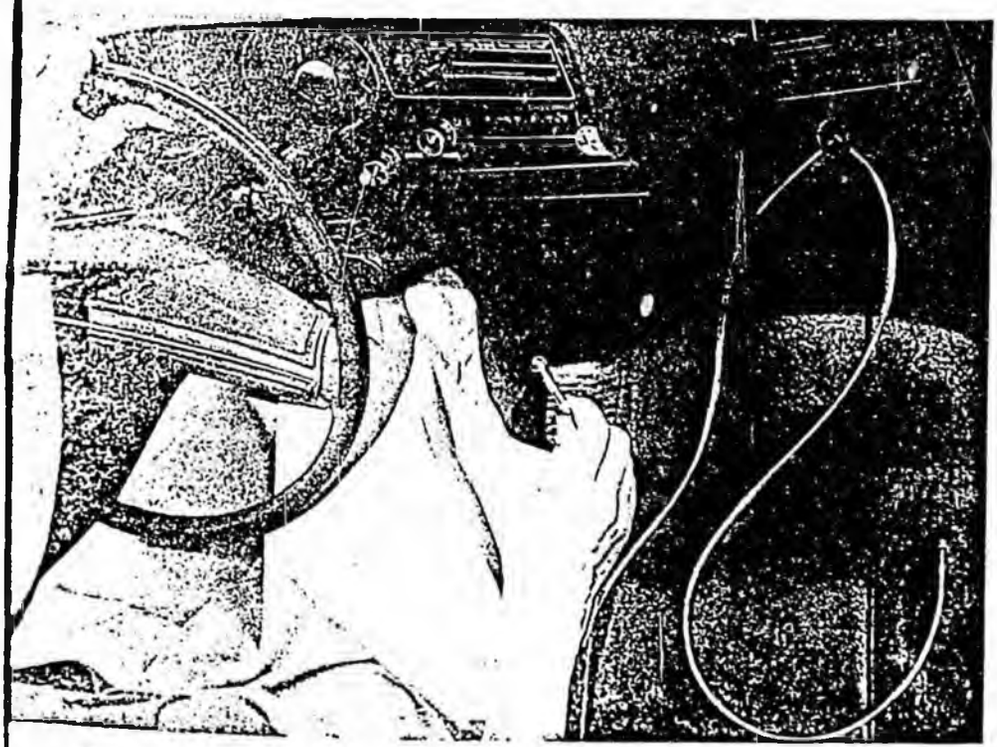
Dr. Heath summed up: "Since the monkeys had received no pot smoke for six months prior to being sacrificed, it is clear that, at least in the limbic area, structural brain changes caused by marijuana are not readily reversible."

Dr. Robert Gilkeson of Cleveland, Ohio, is completing a study of pot-smoking teen-agers which concentrates on EEG readings of the highly developed, cognitive cerebral cortex, or "new brain." Gilkeson specializes in neurophysiologic research and electroencephalography in learning disabilities. In addition to the standard hour-long EEGs, he developed another half-hour of techniques to pinpoint learning disabilities. In a unique on-going study, he has applied this technique to more than 50 youngsters, ages 13 to 18. All come from the affluent suburbs of Cleveland. All said they did not "do" other drugs. All had met the "criteria" of being high on pot at least two or three times a week for the four months preceding the EEG. But all were forbidden to smoke pot for at least 24 hours prior to the test.

Results: *All* EEGs were "markedly immature for age." They also had an abnormal amount of slow theta rhythms, "sufficient," said Gilkeson, "to be diagnostic of diffuse brain impairment. In the EEG section of academic tasks, none of these youngsters could speed up when challenged. Their brain waves failed to respond to these stimuli in the usual way, according to the standardized norms."

Reading the encephalographer's report shocked many youngsters into "getting off the pot." Those who stayed off for three months had normal EEGs when they took the test again. "Of even greater significance," said Gilkeson, "are those who progressed from abnormal to normal with abstinence—and a return to abnormal again when the youngster returned to chronic pot use."

Gilkeson's findings are con-



Dashboard pot pipes enable the smoker to "drive high." More than 50 research studies show that one or two joints seriously impair driving performance, even after the high has gone. Despite this, surveys reveal "60 to 80 percent of users say they sometimes drive while "intoxicated on marijuana."

firmed by a number of other scientists. Dr. Turin Itel, one of the foremost investigators of the effects of drugs on human EEGs, sums up: "Acute or chronic use of marijuana produces an EEG shift toward slow. This is definitely associated with impairment of cognitive functions."

Marijuana and the Lungs

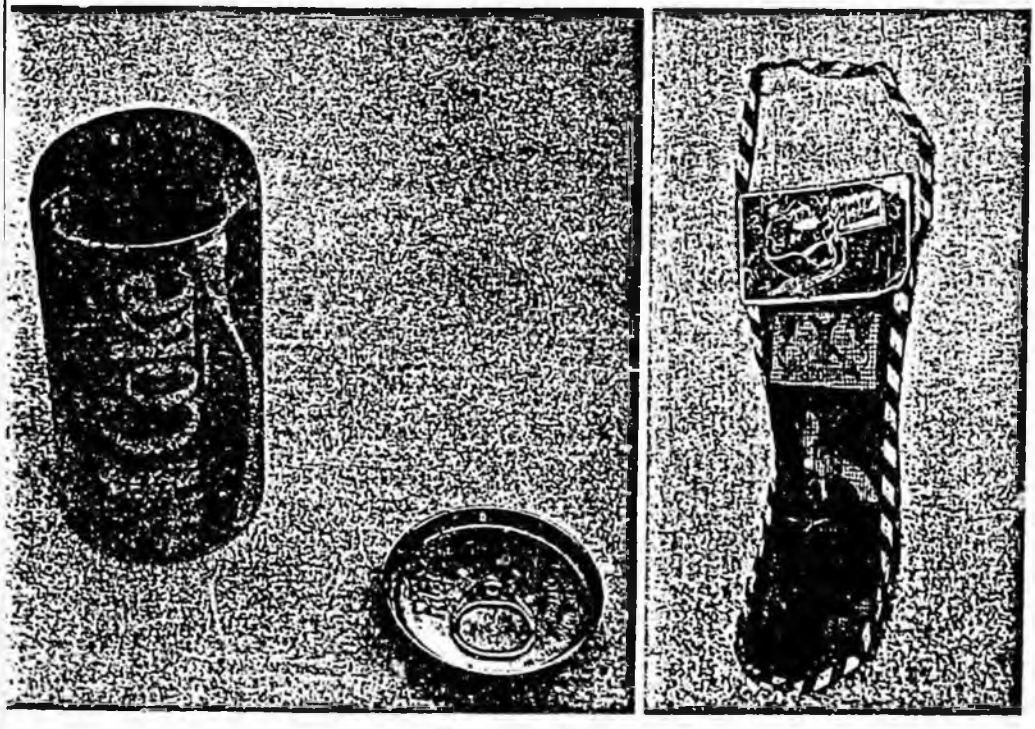
Since pot smoke enters the body through the lungs, it obviously reaches its highest concentration in these organs. A 1975 study compared the compounds in a "weak" marijuana cigarette (.8 percent THC) with a high-tar standard tobacco cigarette. Aside from the fact that tobacco smoke contains nicotine and pot smoke contains cannabinoids, the two types of "smokes" have roughly the same compounds, including lung irritants and carcinogens (cancer-producing agents), co-carcinogens and carcinogen activators. Furthermore, a number of these are present in pot smoke in amounts 50 to 100 percent greater than in tobacco smoke—for example, the carcinogens benzanthracene and benzopyrene, with the latter also being a strong cancer initiator.

In addition to the carcinogens, there are elements in both types of cigarettes which irritate and inflame the lungs. Here, too, marijuana smoke comes out with an even "darker" picture than tobacco smoke. And, whereas tobacco smokers avail themselves of filters, low-tar cigarettes, etc., pot smokers consider "good pot" to be the strongest they can get. In addition, an entire "line" of the drug paraphernalia industry—the "power hitter"—blasts the smoke deep into the lungs. Some power hitters are produced in such kiddie-appealing shapes as red plastic space guns and miniature footballs. Many pot smokers use "bongs" in the belief that drawing the smoke through water or ice lessens the harshness of the smoke by cooling it down. The bong, however, concentrates all the smoke inside a chamber so that none is diffused into the air. As one manufacturer advertises: "The only thing wasted is you."

Pot advocates claim that comparisons between marijuana and tobacco do not hold up, since the tobacco smoker generally puffs on a pack a day or more, whereas the chronic pot smoker may use only one or two joints a day, or less. The noted researcher Dr. Sidney Cohen, who has done one of the three major human studies with marijuana, points out: "There are two factors which equalize the risks involved. First: People—especially young people—are, in fact, smoking more joints per day than ever before [this despite the ever-increasing potency of marijuana available on the streets today]. And it is the younger age groups who seem to be smoking the most.

"Second: Typical tobacco cigarette smokers either do not inhale the smoke into the bronchial passages or, if they do, it is for short periods of time. In contrast, the usual method of smoking marijuana is to inhale the material as deeply as possible, keep it in the lower airways for as long as possible and exhale only when another breath must be taken. At times the inhalation is so complete that no smoke is detectable in the exhaled air.

"This means that not only are the irritants and carcinogens in contact with the actual lung tissue for a longer time, but more of the toxic elements may be absorbed into the bloodstream than is the case with cigarettes. These elements are then delivered to other tissues. New studies show that heavy tobacco smokers are more prone than nonsmokers to cancer of the bladder, the esophagus and other nonpulmonary organs. Presumably, therefore, the carcinogens in both tobacco and marijuana smoke do 'carry.' "



Stash cans for pot come in many guises—and disguises. A popular item: Christmas stockings with candy-flavored rolling papers and pot pipes. Drug paraphernalia has been banned in ten states so far, and the Drug Enforcement Administration's new "model" anti-paraphernalia law is available to all states.

Pot advocates like to point out that "there are no dead bodies from marijuana." With the notable exception of highway accidents caused by stoned drivers, this is true. "However," says Dr. Cohen, "we should not forget that it takes 20 to 30 years of consistent heavy use of tobacco to produce a lung cancer. We have been smoking marijuana heavily in the U.S. for a decade or less. Also, with all our medical sophistication, it was not until the 1950s that we noted any relationship between cigarette smoking and lung cancer.

"In those countries where cannabis has been smoked by adult males for centuries, there have been no long-term longitudinal studies regarding cancer and can-

nabis. Studies have been done, however, which show a high incidence of bronchitis, pharyngitis, etc., among cannabis smokers, especially those who used the stronger varieties."

(In this context, it is interesting to note that in the oft-quoted "Ganja in Jamaica" study of 30 cane workers, lung cells were not analyzed. Furthermore, only healthy people were accepted for the study, thereby excluding those with chronic lung disease. In the words of Dr. John Hall, chairman of the department of medicine in Kingston, "Omitted were all cannabis smokers who showed pathological symptoms such as we see in our clinic." Among other "pathological symptoms" evidenced by long-term "ganja" smokers, Dr. Hall listed emphysema, an irreversible lung disease.)

The 1979 surgeon general's report on tobacco cigarette smoking contained some 30,000 research papers all bearing out the slogan: "The surgeon general warns that cigarette smoking is dangerous to your health." And, based on past statistics, the surgeon general said that "this year alone, cigarettes will kill 346,000 Americans."

Research on marijuana and the lungs is in its infancy compared to that on tobacco and the lungs. But, thus far, the findings are hardly reassuring. For example: Dr. Donald Tashkin, a specialist in pulmonary medicine at UCLA, found a 25 percent increased airflow resistance among pot smokers compared to non-pot smokers. (Airflow determines how well we can get oxygen into our bodies and how well we can get carbon dioxide out.) This was an abnormality which did *not* occur in heavy tobacco smokers.

In studies published in February 1980, Dr. Gary Huber, director of the Smoking and Health Research Program of Harvard University, showed that marijuana activates—by some 200 percent—enzymes which contribute to the "eating" or digesting of the lung itself.

In animal studies where marijuana and tobacco smoke condensates are painted on mouse skin, both produce cancers.

A further gloomy point is that many pot smokers also smoke tobacco cigarettes, and the harmful effects may be additive. Dr. Cohen sums up: "There is real reason for concern that marijuana alone, or marijuana smoked with tobacco, will bring forth a new wave of lung cancer in another 10 to 20 years."

Many people who once believed marijuana to be harmless have now concluded that it may be the most dangerous drug in America today, for many reasons. One such person is Dr. Robert DuPont, chairman of the Drug Dependence Section of the World Psychiatric Association and former federal director of the National Institute on Drug Abuse.

Dr. DuPont says: "I believe it to be our most dangerous drug because of widespread frequent use, especially by our youth, and because the psychological as well as the physical effects are insidious and ultimately devastating. Furthermore, for millions of our youth, marijuana is the gateway to the use of many other illegal drugs, including angel dust, LSD and heroin.

"One of the most disturbing aspects of marijuana use is that the user's judgment about the effects of the drug is clouded by his or her own use of marijuana. If an enemy nation were to plan to undermine America's future, they could not think of a more effective strategy than poisoning our youth. Marijuana is such a poison. The tragedy is more painful because the poison is not being administered by an enemy, but by ourselves. Not only the marijuana-using youth, but all of us as well, must share the responsibility for this tragedy, and we must all participate in combating and overcoming this marijuana plague.

"The one hopeful sign on the horizon is the mobilization of concerned parents. They are distraught—sometimes terrified—by the effects of marijuana on their children. And they are angry at the "professionals" who make them feel that *they* are the problem, rather than the drug. These parents throughout the country are discovering one another and are forming action groups which are beginning to have a positive impact on their own children as well as on our local and national leadership. But parents can't do the job alone. Government, business, educators, media—all segments of our society—must join in a massive endeavor to stop our kids from going to pot."

What Parents Can Do

Three national organizations have spearheaded the movement for "combating" the marijuana plague. The pioneer group in this effort is the American Council on Marijuana, founded in 1977 by the Myrin Institute. On its board were the leading scientists in the field at that time. They developed the first accurate resource materials: scientific information on marijuana for the lay public. Their publication, *Marijuana Today*, by Dr. George Russell, was the first such compilation of medical findings and is now in its fourth updated edition, having sold more than 100,000 copies.

In addition, ACM has held three major conferences at New York University Medical Center and at Columbia University. The second of these, which focused on "Marijuana: Biological Effects and Social Implications," a two-day conference, was the largest gathering of scientists, drug-abuse specialists and educators ever to be held in this country. It was also the first lecture series on marijuana to be accredited by the AMA.

The second organization, also founded in 1977, was PRIDE—Parent Resources and Information on Drug Education—which now has active parent groups in more than 19 states. PRIDE has two main functions: One is to disseminate reliable medical information on the health hazards of marijuana (a "PRIDE Packet" is available to individuals and organizations); the second is to stimulate the organization of new parent groups, using a concept originated by PRIDE—that of developing parent peer pressure groups comprised of the parents of the children's friends (not the parents' friends—these parents may not even know one another) in order to combat teen peer pressure and the "do drug" messages of the "kiddie-youth drug culture." In addition, PRIDE sponsors drug education and prevention conferences for schools, educators and parents to encour-

age them to work together to establish ongoing programs.

The third national organization, Citizens for Informed Choices on Marijuana (CICOM), whose staff helped plan Wellington's "Grass Roots Conference on Grass," has organized similar conferences from Connecticut to Washington.

Lee Dogoloff, White House drug policy advisor, supports the efforts of these groups, saying:

"I truly believe that our brightest hope for the future of hundreds of thousands of young people in the U.S. today is the burgeoning movement of parent/citizen groups now organizing in virtually every state of the nation. There are at this time thousands of adults all working toward the same goal—to see that our children grow up drug-free." ★

Marijuana Reprints

Extra copies of the two marijuana articles which have appeared in *The SatEvePost* may be ordered by enclosing a check or money order as follows:

1 to 9	$1.50 each set of two articles
10 to 99	85¢ each set
100 to 999	65¢ each set
1000 to 1500	40¢ each set

For special bulk purchases, call Susan Hanley at 317-636-8881 for price quotes (any more than 1500).

For reprints, write to: MERF, Dept. M-Reprint, P.O. Box 2166, Indianapolis, IN 46206.

Make your check or money order payable to: MEDICAL EDUCATION AND RESEARCH FOUNDATION.

Check or money order *must* accompany order. Remit in US funds *only*.
Postage is included in the above prices. Special shipping will require additional charges.

Additional References:

American Council on Drug Education, 6193 Executive Boulevard, Rockville, MD 20852. *Marijuana Today,* by George Russell, Ph.D. Medical findings for the layman. $3.00. *Keep Off the Grass,* by Gabriel Nahas, M.D., Ph.D. The marijuana story from 1969 to 1980. $9.50. *Twelve Is Too Old,* by Peggy Mann. The first novel on the pot scene for teens and pre-teens. $7.95.

Committees of Correspondence, Inc., Box 232, Topsfield, MA 01983. (617) 774-2641. *Quarterly Drug Abuse Newsletter* covering an important issue, plus suggestions on what you can do to effect a change. Encourages letter writing. $10 per year. Resource list, pamphlets, etc.

Drug Enforcement Administration: Preventive Programs, Washington, D.C. 20537. (Or GPO, Washington, D.C. 20402.) Excellent 44-page magazine with articles and pictures on health hazards and articles on drug paraphernalia. Single copies free.

Essex County Grand Jury Presentment, Prosecutors' Office, New Courts Building, Newark, NJ 07102. Startling 60-page report on drug abuse in schools, plus Grand Jury's 31 practical mandates (to schools, courts, PTAs, etc.) which can be adopted or adapted by any community. $5.00.

Executive Information Resources, Box 611, Wellington, Kansas 67152. Unedited cassette tapes of the general sessions of the "Grass Roots Conference on Grass" held in Washington. Tapes are priced at $6.40 each or $35.00 for a complete set of seven tapes. Prices include shipping.

Families in Action, 3845 N. Druid Hills Road, Suite 300, Decatur, GA 30033. 164-page book *How to Organize Your Community.* $10.00. Plus quarterly newsletter which includes latest information on the drug scene at state, national and international levels. $10.00.

Logical Communications, Inc., 16 Thorndal Circle, Darien, CT 06820. *How to Help Your Child Resist the Marijuana Culture.* $3.00.

Mini-Courses, 4290 Raintree Lane NW, Atlanta, GA 30327. Six-unit teaching manual, "Drug Abuse and the Growing Child," for third through eighth grades (for schools, homes and agencies). $10.00. Cassette with narration, plus 80 color slides showing youth drug subculture, plus prevention methods. $46.75.

National Federation of Parents for Drug-Free Youth, 1820 Franwall Ave., Suite 16, Silver Spring, MD 20902. (301) 649-7100 or 1-800-554-5437. *Parent/Community Task Force Manual,* $5.00. *Education Kit/Public Speaking Manual,* $5.00. *Press/Media Guidelines,* $4.00. *Organizing a Parent Group,* $2.00. Membership $10.00.

Narcotics Education, Inc., 6830 Laurel St. NW, Washington, D.C. 20012. Six Q & A booklets on marijuana and P.C.P. $2.00. *Listen* (magazine for teens) issue on marijuana. $1.00.

Phoenix House, 164 West 74th St., New York, NY 10023. Free information on drugs, plus advice on school programs.

Prevention Materials Institute, P.O. Box 152, Lafayette, CA 94549. *Communicating About Drugs,* for parents and teachers. $1.75.

PRIDE, 100 Edgewood Ave. NE, Suite 1216, Atlanta, GA 30303. Send for free catalog of publications and audiovisuals.

These organizations cannot process C.O.D. orders.

Medical reprints and health education aids

The Saturday Evening Post, the magazine that helps you to better health, is now making available some of our most requested medical reprints and health education aids.

We have received thousands of letters from Society members requesting these reprints. Now, you can order one, two or the complete set of reprints below at very special membership prices.

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☐ CPR *	Cardiopulmonary resuscitation—CPR—is a life-skill everyone should know. This pamphlet gives you step-by-step instructions $1
☐ Heroes *	An inexpensive food substance as a treatment for heroes? Yes! This booklet has the latest scientific findings $3
☐ Lessen Your Cancer Risk *	A noted oncologist gives you a straightforward report on cancer, its factors and how you can lessen your risks. A national survey form is also included $3
☐ Glaucoma	The silent thief of sight, glaucoma, is exposed in this report contained in the international health newsletter, *Medical Update* $1
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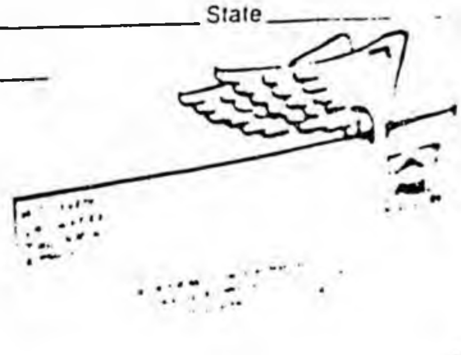

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Marijuana and Health

Compliments of Senator
Paul Fischer

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Marijuana and Health

Report of a Study
by a Committee of the
INSTITUTE OF MEDICINE
Division of Health Sciences Policy

NATIONAL ACADEMY PRESS
Washington, D.C. 1982

NOTICE The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the Councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. The members of the committee responsible for the report were chosen for their special competences and with regard for appropriate balance.

This report has been reviewed by a group other than the authors according to procedures approved by a Report Review Committee consisting of members of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

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This study was supported by the National Institutes of Health, Contract No. NO1-OD-0-2114.

International Standard Book Number 0-309-03236-9

Library of Congress Catalog Card Number 81-86534

Available from:

NATIONAL ACADEMY PRESS
2101 Constitution Ave., N.W.
Washington, D.C. 20418

Printed in the United States of America

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ACKNOWLEDGMENTS

Many persons outside the Institute of Medicine provided helpful suggestions, timely observations, and data bearing on the complex scientific, clinical, and societal issues that were being explored by the committee and staff. We wish especially to express our gratitude for contributions made by Monique Braude, Jacqueline Ludford, Robert Petersen, William Pollin, and Marvin Snyder of the National Institute on Drug Abuse; Edward Tocus and Stuart Nightingale of the Food and Drug Administration; the Interagency Committee to Monitor the Marijuana Study; Carl Leventhal of the National Institutes of Health and the chairman of the Interagency Committee; and Joseph Perpich of the National Institutes of Health, our project officer.

We wish also to acknowledge the many scientists and others who responded to specific requests to review informally a portion of the draft report and those who, in general, gave their active assistance and collaboration:

- C. Wayne Bardin, Population Council
- Neal Benowitz, Langley Porter Psychiatric Institute
- Albert Carlin, University of Washington
- Sidney Cohen, Alcohol Research Center
- Ellen Dempsey, McGill University
- Everett Ellinwood, Duke University Medical Center
- Keith Green, Medical College of Georgia
- Daniel Hoth, National Cancer Institute
- Lloyd Johnston, Institute for Social Research
- Louise Lev, National Cancer Institute
- Markku Linnoila, National Institute of Mental Health
- Oriana Kalant and the Documentation Center of the Addiction Research Foundation
- Edward Khantzian, Cambridge Hospital
- Kaye Kilburn, University of Southern California School of Medicine
- Warren Levinson, University of California, San Francisco
- Raphael Mechoulam, School of Pharmacy, The Hebrew University, Israel
- John Merritt, University of North Carolina

- Akira Morishima, College of Physicians and Surgeons, Columbia University
- Al Munson, Medical College of Virginia
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- Bruce Petersen, Lilly Laboratory for Clinical Research
- Steven Podas, the Mount Sinai Medical Center
- Lee Robins, Washington University Medical School
- Harris Rosenkrantz, EG&G Mason Research Institute
- Donald Tashkin, University of California, Los Angeles
- David Taylor, Centers for Disease Control
- Carlton Turner, Senior Policy Adviser for Drug Policy, Office of Policy Development
- Arthur Zimmerman, University of Toronto

PREFACE

This report is the work of the many people identified in the preceding pages, and to all of them I am very grateful. I particularly wish to thank my distinguished colleagues on the study committee, upon whose expert knowledge and critical judgment this report rests. They responded conscientiously to all the demands placed on them, and they did so with a promptness and grace that made my task easy.

No study of this kind can be carried out without the help of a skilled staff. We were fortunate to have had the assistance of a devoted and highly capable staff team led by Enriqueta C. Bond and Linda S. Dujack. They coordinated the efforts of the committee, the panel, the consultants, and the Institute of Medicine staff, and they played the key role in keeping everything on schedule. Moreover, they carried out this formidable task with tact and common sense. On behalf of the committee, I wish publicly to acknowledge our indebtedness to the IOM staff, and I also wish to express my personal thanks to Drs. Bond and Dujack for their unfailing support and cooperation.

Finally, I wish to acknowledge my appreciation of the editorial assistance of Wallace K. Waterfall, whose expert touch is evident throughout this document. Our aim was to write a report in "a clear and incisive form for the general public." Any success that we may have achieved is due in no small measure to his efforts.

Arnold S. Relman

Arnold S. Relman, M.D.
Chairman

CONTENTS

Marijuana and Health

SUMMARY

The Institute of Medicine (IOM) of the National Academy of Sciences has conducted a 15-month study of the health-related effects of marijuana, at the request of the Secretary of Health and Human Services and the Director of the National Institutes of Health. The IOM appointed a 22-member committee to:

- analyze existing scientific evidence bearing on the possible hazards to the health and safety of users of marijuana;
- analyze data concerning the possible therapeutic value and health benefits of marijuana;
- assess federal research programs in marijuana;
- identify promising new research directions, and make sugggestions to improve the quality and usefulness of future research; and
- draw conclusions from this review that would accurately assess the limits of present knowledge and thereby provide a factual, scientific basis for the development of future government policy.

This assessment of knowledge of the health-related effects of marijuana is important and timely because marijuana is now the most widely used of all the illicit drugs available in the United States. In 1979, more than 50 million persons had tried it at least once. There has been a steep rise in its use during the past decade, particularly among adolescents and young adults, although there has been a leveling-off in its overall use among high school seniors in the past 2 or 3 years and a small decline in the percentage of seniors who use it frequently. Although substantially more high school students have used alcohol than have ever used marijuana, more high school seniors use marijuana on a daily or near-daily basis (9 percent) than alcohol (6 percent). Much of the heavy use of marijuana, unlike alcohol, takes place in school, where effects on behavior, cognition, and psychomotor performance can be particularly disturbing. Unlike alcohol, which is rapidly metabolized and eliminated from the body, the psychoactive components of marijuana persist in the body for a long time. Similar to alcohol, continued use of marijuana may cause tolerance and dependence. For all these reasons, it is imperative that we have reliable and detailed

information about the effects of marijuana use on health, both in the long and short term.

What, then, did we learn from our review of the published scientific literature? Numerous acute effects have been described in animals, in isolated cells and tissues, and in studies of human volunteers; clinical and epidemiological observations also have been reported. This information is briefly summarized in the following paragraphs.

EFFECTS ON THE NERVOUS SYSTEM AND ON BEHAVIOR

We can say with confidence that marijuana produces acute effects on the brain, including chemical and electrophysiological changes. Its most clearly established acute effects are on mental functions and behavior. With a severity directly related to dose, marijuana impairs motor coordination and affects tracking ability and sensory and perceptual functions important for safe driving and the operation of other machines; it also impairs short-term memory and slows learning. Other acute effects include feelings of euphoria and other mood changes, but there also are disturbing mental phenomena, such as brief periods of anxiety, confusion, or psychosis.

There is not yet any conclusive evidence as to whether prolonged use of marijuana causes permanent changes in the nervous system or sustained impairment of brain function and behavior in human beings. In a few unconfirmed studies in experimental animals, impairment of learning and changes in electrical brain-wave recordings have been observed several months after the cessation of chronic administration of marijuana. In the judgment of the committee, widely cited studies purporting to demonstrate that marijuana affects the gross and microscopic structure of the human or monkey brain are not convincing; much more work is needed to settle this important point.

Chronic relatively heavy use of marijuana is associated with behavioral dysfunction and mental disorders in human beings, but available evidence does not establish if marijuana use under these circumstances is a cause or a result of the mental condition. There are similar problems in interpreting the evidence linking the use of marijuana to subsequent use of other illicit drugs, such as heroin or cocaine. Association does not prove a causal relation, and the use of marijuana may merely be symptomatic of an underlying disposition to use psychoactive drugs rather than a "stepping stone" to involvement with more dangerous substances. It is also difficult to sort out the relationship between use of marijuana and the complex symptoms known as the amotivational syndrome. Self-selection and effects of the drug are probably both contributing to the motivational problems seen in some chronic users of marijuana.

Thus, the long-term effects of marijuana on the human brain and on human behavior remain to be defined. Although we have no convincing evidence thus far of any effects persisting in human beings after cessation of drug use, there may well be subtle but important physical and psychological consequences that have not been recognized.

EFFECTS ON THE CARDIOVASCULAR AND RESPIRATORY SYSTEMS

There is good evidence that the smoking of marijuana usually causes acute changes in the heart and circulation that are characteristic of stress, but there is no evidence to indicate that a permanently deleterious effect on the normal cardiovascular system occurs. There is good evidence to show that marijuana increases the work of the heart, usually by raising heart rate and, in some persons, by raising blood pressure. This rise in workload poses a threat to patients with hypertension, cerebrovascular disease, and coronary atherosclerosis.

Acute exposure to marijuana smoke generally elicits bronchodilation; chronic heavy smoking of marijuana causes inflammation and pre-neoplastic changes in the airways, similar to those produced by smoking of tobacco. Marijuana smoke is a complex mixture that not only has many chemical components (including carbon monoxide and "tar") and biological effects similar to those of tobacco smoke, but also some unique ingredients. This suggests the strong possibility that prolonged heavy smoking of marijuana, like tobacco, will lead to cancer of the respiratory tract and to serious impairment of lung function. Although there is evidence of impaired lung function in chronic smokers, no direct confirmation of the likelihood of cancer has yet been provided, possibly because marijuana has been widely smoked in this country for only about 20 years, and data have not been collected systematically in other countries with a much longer history of heavy marijuana use.

EFFECTS ON THE REPRODUCTIVE SYSTEM AND ON CHROMOSOMES

Although studies in animals have shown that Δ-9-THC (the major psychoactive constituent of marijuana) lowers the concentration in blood serum of pituitary hormones (gonadotropins) that control reproductive functions, it is not known if there is a direct effect on reproductive tissues. Delta-9-THC appears to have a modest reversible suppressive effect on sperm production in men, but there is no proof that it has a deleterious effect on male fertility. Effects on human female hormonal function have been reported, but the evidence is not convincing. However, there is convincing evidence that marijuana interferes with ovulation in female monkeys. No satisfactory studies of the relation between use of marijuana and female fertility and child-bearing have been carried out. Although Δ-9-THC is known to cross the placenta readily and to cause birth defects when administered in large doses to experimental animals, no adequate clinical studies have been carried out to determine if marijuana use can harm the human fetus. There is no conclusive evidence of teratogenicity in human offspring, but a slowly developing or low-level effect might be undetected by the studies done so far. The effects of marijuana on reproductive function and on the fetus are unclear; they may prove to be negligible, but further research to establish or rule out such effects would be of great importance.

Extracts from marijuana smoke particulates ("tar") have been found to produce dose-related mutations in bacteria; however, Δ-9-THC, by itself, is not mutagenic. Marijuana and Δ-9-THC do not appear to break chromosomes, but marijuana may affect chromosome segregation during cell division, resulting in an abnormal number of chromosomes in daughter cells. Although these results are of concern, their clinical significance is unknown.

THE IMMUNE SYSTEM

Similar limitations exist in our understanding of the effects of marijuana on other body systems. For example, some studies of the immune system demonstrate a mild, immunosuppressant effect on human beings, but other studies show no effect.

THERAPEUTIC POTENTIAL

The committee also has examined the evidence on the therapeutic effects of marijuana in a variety of medical disorders. Preliminary studies suggest that marijuana and its derivatives or analogues might be useful in the treatment of the raised intraocular pressure of glaucoma, in the control of the severe nausea and vomiting caused by cancer chemotherapy, and in the treatment of asthma. There also is some preliminary evidence that a marijuana constituent (cannabidiol) might be helpful in the treatment of certain types of epileptic seizures, as well as for spastic disorders and other nervous system diseases. But, in these and all other conditions, much more work is needed. Because marijuana and Δ-9-THC often produce troublesome psychotropic or cardiovascular side-effects that limit their therapeutic usefulness, particularly in older patients, the greatest therapeutic potential probably lies in the use of synthetic analogues of marijuana derivatives with higher ratios of therapeutic to undesirable effects.

THE NEED FOR MORE RESEARCH ON MARIJUANA

The explanation for all of these unanswered questions is insufficient research. We need to know much more about the metabolism of the various marijuana chemical compounds and their biologic effects. This will require many more studies in animals, with particular emphasis on subhuman primates. Basic pharmacologic information obtained in animal experiments will ultimately have to be tested in clinical studies on human beings.

Until 10 or 15 years ago, there was virtually no systematic, rigorously controlled research on the human health-related effects of marijuana and its major constituents. Even now, when standardized marijuana and pure synthetic cannabinoids are available for experimental studies, and good qualitative methods exist for the

measurement of Δ-9-THC and its metabolites in body fluids, well-designed studies on human beings are relatively few. There are difficulties in studying the clinical effects of marijuana in human beings, particularly the effects of long-term use. And yet, without such studies the debate about the safety or hazard of marijuana will remain unresolved. Prospective cohort studies, as well as retrospective case-control studies, would be useful in identifying long-term behavioral and biological consequences of marijuana use.

The federal investment in research on the health-related effects of marijuana has been small, both in relation to the expenditure on other illicit drugs and in absolute terms. The committee considers the research particularly inadequate when viewed in light of the extent of marijuana use in this country, especially by young people. We believe there should be a greater investment in research on marijuana, and that investigator-initiated research grants should be the primary vehicle of support.

The committee considers all of the areas of research on marijuana that are supported by the National Institute on Drug Abuse to be important, but we did not judge the appropriateness of the allocation of resources among those areas, other than to conclude that there should be increased emphasis on studies in human beings and other primates. Recommendations for future research are presented at the end of Chapters 3-7 of this report.

CONCLUSIONS

The scientific evidence published to date indicates that marijuana has a broad range of psychological and biological effects, some of which, at least under certain conditions, are harmful to human health. Unfortunately, the available information does not tell us how serious this risk may be.

Our major conclusion is that what little we know for certain about the effects of marijuana on human health--and all that we have reason to suspect--justifies serious national concern. Of no less concern is the extent of our ignorance about many of the most basic and important questions about the drug. Our major recommendation is that there be a greatly intensified and more comprehensive program of research into the effects of marijuana on the health of the American people.

INTRODUCTION

The Institute of Medicine (IOM) of the National Academy of Sciences has undertaken this review and analysis of the health-related effects of marijuana* at the request of the Secretary of the Department of Health and Human Services (DHHS) and the Director of the National Institutes of Health (NIH).

Scientific controversy and public confusion about marijuana continue unabated and perhaps even are expanding, notwithstanding numerous reports on the topic from authoritative agencies and organizations (Fifth, Sixth, Seventh, and Eighth Annual Reports from the Secretary of Health, Education and Welfare to the Congress on Marijuana and Health; Fehr, et al., Cannabis: Adverse Effects on Health, 1980a; Tinklenberg, Marijuana and Health Hazards and Marijuana in the '80s, a report of the Council on Scientific Affairs, the American Medical Association, 1980). Increasing use of this substance and growing concern about its possible long- and short-term consequences for human health have added some urgency to the need for reassessment of the available data. Interest has been further heightened by recent suggestions that marijuana may also have some medical therapeutic value, which only intensifies the debate about what our public policy towards marijuana ought to be.

With this as background, the Secretary of Health, Education, Welfare, Joseph A. Califano, Jr., in a press statement on April [illegible] 1979, announced the intention of his department to undertake a review that would ". . . assess the information and scientific work now available on the effects of marijuana." He followed that with a memorandum on May 16, 1979, to Donald S. Fredrickson, Director of NIH in which he further stated:

> This review must be undertaken by an independent scientific body that has not staked out a position in this highly controversial field. This review should be conducted by a

*The terms marijuana and cannabis will be used interchangeably in this report. Strictly speaking, they are not synonymous; cannabis is the more general term. (See Glossary, page 9.)

> group of distinguished biomedical and clinical scientists and should involve thorough, systematic review and analysis of the research literature. . . . The report should identify the most urgently needed and promising lines of inquiry to build a firmer base for decision-making in years to come. The information should be available in a clear and incisive form for the general public.
>
> While the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA) and its National Institute on Drug Abuse (NIDA) have provided leadership in research related to biological and health effects of marijuana, it is most important that we have a review by an independent nongovernmental body, such as the Institute of Medicine. In order to avoid even the appearance of a conflict of interest, inasmuch as this review will cover part of the research plan of ADAMHA-NIDA, I believe it is important that the National Institutes of Health serve as the responsible DHHS agency for seeing that such a review is conducted.

Following Mr. Califano's resignation, subsequent secretaries have confirmed to the Director of the NIH their desire to see this review carried forward. Accordingly, a contract between the NIH and the IOM was executed to provide for a study to commence September 30, 1980, and be completed by December 29, 1981.

THE COMMITTEE'S TASK

Under this contract, the IOM agreed to appoint a committee to:

1. analyze existing scientific evidence bearing on the possible hazards to the health and safety of users of marijuana;
2. analyze data concerning the possible therapeutic value and health benefits of marijuana;
3. assess federal research programs in this area;
4. identify promising new research directions, and make suggestions to improve the quality and usefulness of future research;
5. draw conclusions from this review that would accurately assess the limits of present knowledge and thereby provide a factual, scientific basis for the development of future government policy. Such an assessment also should be helpful to private citizens who want to make their own informed decisions about this subject.

The committee's charge specifically excluded the analysis or formulation of public policy.

PROCEDURE FOR THE STUDY

Primary responsibility for the conduct of the study was vested in a steering committee of 22 biologists, behavioral scientists, and

INTRODUCTION

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clinicians. Although they all were experts in relevant disciplines, only a few had previously been involved in the study of marijuana or had taken public positions on the subject. The committee was divided into six panels, each concerned with major scientific areas: cardiovascular and respiratory system effects; neurobiological effects; epidemiological, behavioral, and psychosocial effects; reproductive biology and effects on the fetus; pharmacology, cell biology, and immunology; and genetic and oncogenic effects. Each panel was chaired by a member of the committee and usually had one or more additional committee members and several expert consultants, whose names appear in the front of this report. The committee also consulted with many other experts in the course of its work and received valuable help from many persons and organizations.

The full committee met five times to coordinate and assess its progress. In the intervals between these meetings, the panels held their own independent sessions and various ad hoc working groups met as necessary. The chairman and members of the committee staff were invited observers at the Conference on Adverse Health and Behavioral Consequences of Cannabis Use, which was sponsored by the Addiction Research Foundation (ARF) of Ontario and the World Health Organization (WHO) and held in Toronto, Canada, from March 30 to April 3, 1981. Other members of our committee served as working members of that conference. We were also fortunate in being able to work closely with members of the ARF/WHO conference staff and having access to all the documents prepared for the Canadian meeting as well as the revised draft of the summary report of the conference (1981).

The committee began by systematically reviewing all the literature published since 1975 on marijuana and related subjects, which had been collected by our staff through a Medline computer search. Earlier literature was selectively examined, as were a variety of other documents, reviews, and monographs on the subject. Our objective was not merely to compile and summarize, but also to evaluate the evidence critically and, with the aid of our consultants, form some judgment of the quality and reliability of the work. Our report is an assessment of what is and is not known, based on our best interpretations of the scientific literature. We confined our attention to published scientific articles as the primary sources of information, relying heavily on experts in each field to select the relevant papers and help us interpret the data.

To obtain additional information and opinions from the public and from professional groups on the health-related effects of marijuana, we solicited written responses in a notice in the Federal Register of February 24, 1981. Responses were received and incorporated into the records of the committee. (See Appendix A for a complete description.) The responses fell into three categories:

1. The dangers of marijuana. Letters in this category came from mothers whose children were using or had used marijuana. These parents believed that drug use by their children led to a lack of motivation and loss of interest in school and other activities. Letters about the harmfulness of the use of marijuana were also received from physicians and scientists.

2. The therapeutic potential of marijuana. Half of the responses were from people who used marijuana illegally for various medical problems and who urged that it be made easily available to patients. Several letters submitted by legislators and doctors described problems in obtaining marijuana for therapeutic use (see Appendix B). A group interested in the legitimate medical use of cannabis emphasized the need for continuing investigation into the numerous constituents of the marijuana plant for therapeutic uses.

3. Support of general use and legalization of marijuana. Letters were received from individuals and groups favoring the use of marijuana and actively promoting its legalization.

This report covers most of the concerns expressed by the public, except the question of legalization. The various statements included many opinions and much anecdotal evidence from laymen and scientists. The committee took note of this material, but has not cited any of it in this report unless it was supported by published data in the scientific literature.

THE ORGANIZATION OF THE REPORT

This report is divided into eight chapters and a summary. The summary includes the principal findings and conclusions of the study, together with suggestions for future research.

The first chapter reviews what is known about the chemistry and pharmacology of marijuana. Chapter 2 deals with the epidemiology and demography of the use of marijuana in the United States. The next three chapters discuss the effects of marijuana on cells, tissues, organs, and biological systems. Chapter 6 deals with behavioral and psychosocial effects. Chapter 7 discusses the present status of marijuana as a therapeutic agent. Chapter 8 describes and analyzes the federal research program on marijuana.

This report is intended to be intelligible to readers who are not expert on the subjects at hand. We have tried to use technical language only where accuracy would be compromised by less precise terms, and to keep the discussions as brief and as clearly stated as is consistent with our obligation to present a valid critique of the state of knowledge in this field. Although we have surveyed the literature as thoroughly as possible, our citations are selective rather than exhaustive, because they are intended to illustrate or document only the key points in the discussion. For comprehensive bibliographies, see Waller et al., 1976; Abel, 1979; and Kalant et al., 1980.

GLOSSARY OF TERMS FOR MARIJUANA-RELATED PRODUCTS

CANNABIDIOL (CBD) and CANNABINOL (CBN) are major cannabinoids generally present in cannabis (see CANNABIS and CANNABINOIDS).

CANNABINOIDS are a class of 21-carbon compounds present in Cannabis sativa. The basic structure contains a six-membered hydroaromatic ring and a benzene ring joined by a pyran moiety (see Figure 1-1 in Chapter 1). Derivatives include a number of carboxylic acids, their analogues, and transformation products.

CANNABIS is a general term for any of the various preparations of the plant Cannabis sativa and the cannabinoids obtained from it. "Cannabinoid" is a generic term for a class of compounds. Cannabis sativa, also called hemp, is an herbaceous annual plant that readily grows in temperate climates. Depending on the geographic region, and other considerations, the various natural preparations of cannabis possess different physical characteristics and concentrations of cannabinoids. Cannabis preparations may contain over 420 different compounds; of these, 61 have been identified as cannabinoids, many of which possess some biological activity. Marijuana, hashish, and tetrahydrocannabinol are examples of different forms or components of cannabis.

HASHISH is a resin, generally more potent than marijuana, which is obtained from Cannabis sativa by shaking, pressing, or scraping the leaves and flowers of the plant and usually contains some of the latter.

MARIJUANA is a general term for crude preparations obtained from the plant Cannabis sativa and is a mixture of crushed leaves, twigs, seeds, and sometimes the flowers of this plant. In the United States, the term "marijuana" has often been used interchangeably with cannabis to refer to any part of the plant or extract therefrom or any of the synthetic cannabinoids that induce somatic and psychic changes in man.

SINSEMILLA is a seedless variety of high-potency marijuana, originally grown in California.

TETRAHYDROCANNABINOL (THC) is one of the major groups of cannabinoids. Delta-9-THC is the principal active constituent in natural cannabis preparations. Delta-9-THC is also known as Δ-1-THC, by a different system of nomenclature. (In the United States, the Δ-9-THC content of marijuana ranges from unmeasurable amounts to about 6 percent.) Another active isomer, Δ-8-THC, is less often present in marijuana and typically occurs in minute amounts. Many derivatives of Δ-9-THC have been synthesized.

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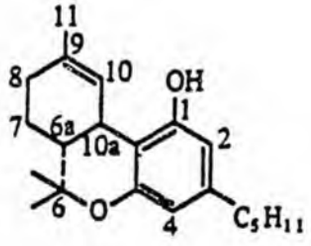
I

CHEMISTRY AND PHARMACOLOGY OF MARIJUANA

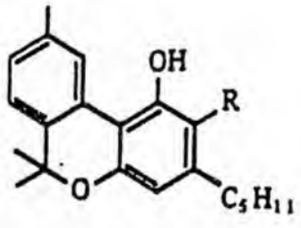
The cannabis plant (Cannabis sativa) thrives under a variety of growing conditions. It has been cultivated for centuries, mainly for hemp fiber, but also for its psychoactive and putative medicinal properties (Abel, 1980; Turner et al., 1980). Although the behavioral and psychological effects were well described in literature of the nineteenth century (Kalant and Kalant, 1968), the complex chemistry and pharmacology of the cannabis plant discouraged extensive investigation until about 15 years ago.

The most prominent effects of cannabis are on psychological phenomena and behavior. Psychopharmacology and behavioral pharmacology have developed as divisions of scientific inquiry only over the past 25 years; therefore, the older cannabis literature, no matter how valuable for observations on other matters, does not provide a basis for quantitative pharmacological analysis and evaluation.

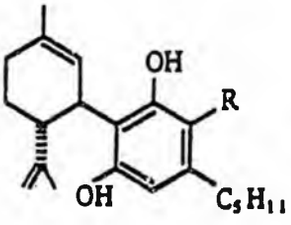
Early pharmacologists could work only with crude extracts of the plant. Although the general structure of the cannabinoids (Figure 1) was known by the turn of the century, the particular cannabinoids that were identified early and were available as pure substances were largely devoid of the characteristic psychoactive and other pharmacological effects of cannabis. Synthetic cannabinoids with cannabislike activity became available in the 1930s. It was not until 1964 that an active ingredient of cannabis was identified as Δ-9-tetrahydrocannabinol (THC) and synthesized (Figure 1) (Gaoni and Mechoulam, 1964; Mechoulam and Gaoni, 1965, 1967). In the mid-1960s, the isolation and synthesis of the main psychoactive component of cannabis and related cannabinoids, together with a rapid increase in the use of marijuana by middle class North American students, stimulated scientific activity (Waller et al., 1976; Waller et al., in press). This chapter, an overview of cannabis chemistry and pharmacology, emphasizes difficulties in the study of this drug (explored further in subsequent chapters) and in evaluating the literature.



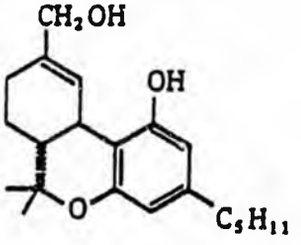
Δ-9-THC



Cannabinol



Cannabidiol



11-hydroxy-Δ-9-THC

FIGURE 1 Cannabinoid structures.

CANNABIS CHEMISTRY

Chemistry of the Plant

Cannabis, the crude material from the plant Cannabis sativa, contains hundreds of chemicals. Most of these are found in other plants, but 61, termed cannabinoids, are unique to the cannabis plant (Table 1). Natural and most synthetic cannabinoids are relatively insoluble in water, but dissolve in fats and fat solvents and are therefore called lipid soluble.

A single cannabinoid, Δ-9-THC, produces almost all the characteristic specific pharmacological effects of the complex, crude cannabis mixtures. A number of synthetic cannabinoids have pharmacological effects similar to Δ-9-THC. Other cannabinoids in the plant, for example, cannabinol (Figure 1), are almost inactive pharmacologically or may interact with Δ-9-THC to modify its actions. One cannabinoid, cannabidiol (CBD), can influence the metabolism of another, Δ-9-THC (Siemens et al., 1976). A few cannabinoids have effects quite different from Δ-9-THC. For example, cannabidiol (Figure 1) has relatively little psychoactive and cardiovascular effect but is an active anticonvulsant (Karler and Turkanis, 1981).

Investigators have chemically altered the Δ-9-THC molecule in an attempt to determine which of its structural elements are required to produce behavioral or other effects (Mechoulam et al., 1980). Studies of structure-activity relationships indicate that, to produce

TABLE 1 Chemical Constituents of Cannabis Preparations

1. Cannabinoids: 61 known
   a. Cannabigerol (CBG) type: 6 known
   b. Cannabichromene (CBC) type: 4 known
   c. Cannabidiol (CBD) type: 7 known
   d. Δ-9-Tetrahydrocannabinol (Δ-9-THC) type: 9 known
   e. Δ-8-Tetrahydrocannabinol (Δ-8-THC) type: 2 known
   f. Cannabicyclol (CBL) type: 3 known
   g. Cannabielsoin (CBE) type: 3 known
   h. Cannabinol (CBN) type: 6 known
   i Cannabinodiol (CBND) type: 2 known
   j. Cannabitriol (CBT) type: 6 known
   k. Miscellaneous types: 9 known
   l. Other cannabinoids: 4 known
2. Nitrogenous compounds: 20 known
3. Amino acids: 18 known
4. Proteins, glycoproteins, and enzymes: 9 known
5. Sugars and related compounds: 34 known
6. Hydrocarbons: 50 known
7. Simple alcohols: 7 known
8. Simple aldehydes: 12 known
9. Simple ketones: 13 known
10. Simple acids: 20 known
11. Fatty acids: 12 known
12. Simple esters and lactones: 13 known
13. Steroids: 11 known
14. Terpenes: 103 known
15. Noncannabinoid phenols: 16 known
16. Flavanoid glycosides: 19 known
17. Vitamins: 1 known
18. Pigments: 2 known

SOURCE: Adapted from Turner, 1980.

effects on behavior, a pyran ring must be part of the three-ring system, a free phenolic hydroxyl on the aromatic ring at C-1, and a lipophilic side chain (C_5H_{11}) at C-3 (Figure 1). Understanding chemical structure-effect relationships is important to guide the synthesis of cannabinoids with differing pharmacological effects. Different effects of Δ-9-THC activity by chemical design will require further syntheses and pharmacological study of a large number of cannabinoids.

Chemistry of the Smoke

It is impossible to understand the effects of cannabis without quantitative control of the composition and the amount of the active substances, that is, control over the dose. Systematic pharmacology must therefore be performed using pure compounds. In the United States, cannabis usually is smoked, which complicates the pharmacology.

The smoke from any burning plant contains hundreds of chemicals that may have biological effects. This poses a dilemma for researchers, because consequences of smoking cannabis cannot be fully determined by studies only of the pure cannabinoids. Studies also are needed with doses of Δ-9-THC delivered, however imperfectly, by smoking.

The dose of Δ-9-THC obtained from smoking cannabis varies greatly, depending on many factors (Table 2). First, the content of Δ-9-THC depends on the genetic background or phenotype of the plant, the sex of the plant, conditions of growth and storage, and the plant preparation smoked. Second, much of the Δ-9-THC in fresh leaves that can be detected by gas-liquid chromatography (GLC) is in inactive carboxylated form. Decarboxylation to the active Δ-9-THC occurs slowly during storage and rapidly during heating, such as occurs in smoking or GLC analysis. Third, the way in which a cigarette is smoked can greatly affect how much of the Δ-9-THC content is absorbed by the smoker.

Cannabis smoke is similar to tobacco smoke in that it is a mixture of very small particles and a gas-vapor phase. Both the particulate and vapor phases contain many identified and probably some still unidentified constituents that, based on clinical experience with tobacco smoke, must be assumed to be potentially harmful (Leuchtenberger and Leuchtenberger, 1976). The amounts of some materials in tobacco cigarette and marijuana cigarette smoke are compared in Table 3. Toxic substances, such as carbon monoxide, hydrogen cyanide, and nitrosamines occur in similar concentrations in tobacco and marijuana smoke; so do the amounts of the particulate material known collectively as "tars."

It is not easy to compare the toxicity of a given number of marijuana cigarettes to a given number of tobacco cigarettes. There are general similarities in the composition of the smoke, but the variations in composition of both tobacco and marijuana cigarettes and differences in smoking techniques make simple extrapolations of risks of tobacco versus marijuana smoking not valid.

TABLE 2 Concentrations of Δ-9-THC in Different Varieties of Marijuana

Type	Percent Δ-9-THC (Percent by Weight)	Normalized Averages[e]
Nepal[c]	2.81	
Mexico[c]	1.68	1.00
Pakistan[c]	1.30	
Colombia[e]		3.00-3.50
India[f]	0.46 (grown above 2000 m)	
	1.39 (grown below 2000 m)	
Jamaica (Ganja)[h]	2.80 (mean)	
United States[c]	0.35	
Sinsemilla (fiber)[d]	0.21	
Sinsemilla (intermediate)[d]	3.58	
Sinsemilla (drug)[d]	6.28	3.00-11.00
Hashish (U.N. standard)[d]	2.22 (7.40)[b]	1.90
NIDA (cigarette 1)[d]	0.84	
NIDA (cigarette 2)[d]	1.86 (2.8)[g]	
Crude marijuana extract[g]	20.00	
Illicit hashish oil[g]	10.00-30.00 (up to 60)[a]	20.00
Research harvest[g]	0.90-2.80	

SOURCES: (a) Jones, 1980; (b) Braenden, 1972; (c) Turner, 1974; (d) Turner, 1980; (e) Turner, 1981; (f) Turner et al., 1979; (g) Rosenkrantz, 1981; (h) Marshman et al., 1976.

TABLE 3 Marijuana and Tobacco Reference Cigarette Analysis of Mainstream Smoke

	Marijuana Cigarette (85 mm)	Tobacco Cigarette (85 mm)
A. Cigarettes		
Average weight, mg	1115	1110
Moisture, percent	10.3	11.1
Pressure drop, cm	14.7	7.2
Static burning rate, mg/s	0.88	0.80
Puff number	10.7	11.1
B. Mainstream smoke		
I. Gas phase		
Carbon monoxide, vol. percent	3.99	4.58
mg	17.6	20.2
Carbon dioxide, vol. percent	8.27	9.38
mg	57.3	65.0
Ammonia, µg	228	199
HCN, µg	532	498
Cyanogen $(CN)_2$, µg	19	20
Isoprene, µg	83	310
Acetaldehyde, µg	1200	980
Acetone, µg	443	578
Acrolein, µg	92	85
Acetonitrile, µg	132	123
Benzene, µg	76	67
Toluene, µg	112	108
Vinyl chloride, ng[a]	5.4	12.4
Dimethylnitrosamine, ng[a]	75	84
Methylethylnitrosamine, ng[a]	27	30
pH, third puff	6.56	6.14
fifth puff	6.57	6.15
seventh puff	6.58	6.14
ninth puff	6.56	6.10
tenth puff	6.58	6.02
II. Particulate phase		
Total particulate matter, dry, mg	22.7	39.0
Phenol, µg	76.8	138.5
o-Cresol, µg	17.9	24
m- and p-Cresol, µg	54.4	65
Dimethylphenol, µg	6.8	14.4
Catechol, µg	188	328
Cannabidiol, µg	190	-
Δ^9-Tetrahydrocannabinol, µg	820	-
Cannabinol, µg	400	-
Nicotine, µg	-	2850
N-Nitrosonornicotine, ng[a]	-	390
Naphthalene, µg	3.0	1.2
1-Methylnaphthalene, µg	6.1	3.65
2-Methylnaphthalene	3.6	1.4
Benz(a)anthracene, ng[a]	75	43
Benzo(a)pyrene, ng[a]	31	21.1

[a]Indicates known carcinogens.
SOURCES: Hoffmann et al., 1975, 1976; Brunnemann et al., 1976, 1977.

Other Preparations

Besides the crude plant leaf material for smoking, usually called marijuana, resinous material from the plant, called hashish, and solvent extracts of the plant, termed hashish oil, sometimes appear on the illicit market. In many parts of the world, hashish is more commonly used than marijuana. As with all cannabis preparations, the Δ-9-THC content of hashish varies enormously, but the upper limits of Δ-9-THC content are usually much higher than for marijuana: 7 percent or higher and even higher for hashish oil (Table 2). However, even these generally more potent forms of cannabis may occasionally contain much less Δ-9-THC.

The mere designation of the nature of a cannabis preparation is an unreliable predictor of its Δ-9-THC content. The practical consequence of this for the clinical researcher is that the exposure to cannabis users is not known.

What Potency of Marijuana Is Available From Street Samples?

Because of the many confounding variables mentioned above, it is difficult to know what potency of psychoactive drug is in marijuana sold illicitly. The concentration of Δ-9-THC in a given sample will vary (Ritzlin et al., 1979). The content of Δ-9-THC from various street samples has been assayed. Marijuana from Drug Enforcement Administration confiscated samples; samples received through psychiatrists, police departments; and state crime laboratories, and fugitive* samples were quantitatively analyzed for Δ-9-THC and other cannabinoids. A physical description of the sample was made--e.g., buds, sinsemilla. The plants were also categorized by origin--where they were cultivated. The analysis showed that tremendous variability exists in the potency of Δ-9-THC on the street; normalized samples ranged from zero to 11 percent Δ-9-THC (Turner, 1981).

Analytic Methods

Detection and measurement of cannabinoids and their metabolites in body fluids is far more difficult than with such drugs as alcohol. The blood and tissue levels resulting from use of ordinary cannabis are very low--nanograms† per milliliter or lower. In addition, compounds like steroids, occurring normally in body fluids interfere with the measurement of cannabinoids in blood and can make the test much less sensitive than if pure cannabinoids in an uncontaminated

*Samples received, when no arrests were made.
†one billionth of a gram.

solution are being analyzed (Harvey et al., 1980; Harvey and Paton, 1980).

A combination of gas-liquid chromatography and mass spectrometry is the most sensitive direct method of measuring cannabinoids. That, however, requires skilled technicians and expensive equipment not readily available. Using modifications of this experimental technique, one can measure as little as 5 picograms* of Δ-9-THC in a milliliter of plasma (Harvey et al., 1980; Harvey and Paton, 1980). Radioimmunoassay and enzyme immunoassay techniques also are available, the lower limits of sensitivity of these methods now are not adequate for reliable measurements of Δ-9-THC in human blood more than a few hours after drug administration. A readily available enzyme immunoassay will detect cannabis metabolites in the urine for as long as a week after the smoking of a single marijuana cigarette. Thus, a positive urine test by this method is not necessarily indicative of use within the previous few hours and does not provide evidence of recent intoxication as a breath test does for alcohol. Assays for cannabinoids are likely to remain far more complicated than for alcohol and many other drugs.

PHARMACOLOGY OF CANNABIS

Implicit in a discussion of the effects of any drug is some determination of dose. The intensity and duration of effects in relation to drug dose must be determined or inferred from adequate pharmacologic study. The intensity and duration of a drug effect depends on at least three major factors:

1. The concentration of the drug at the sites of action in the body. This is determined by the dose, what the drug is dissolved in or mixed with, the route of administration, and the pharmacokinetics of the drug.
2. The sensitivity of the cells the drug acts upon.
3. The physiological state of the bodily systems being affected. This, in turn, depends on interactions with other systems and, especially for drugs with behavioral and psychological effects, as well as environmental and experiential factors, including the presence of other drugs.

With cannabis, many or even most of these factors are not always measurable or under the control of an investigator.

*1 pg = 10^{-12} grams.

Potency and Pharmacokinetic Considerations

Pharmacokinetic studies of the absorption, distribution, metabolism, and elimination of Δ-9-THC determine how long Δ-9-THC and its metabolites remain in the body. Pharmacokinetics vary with the route of drug administration and such factors as lipid solubility; Δ-9-THC tends to remain for long periods of time in fatty tissue.

When smoked, Δ-9-THC is rapidly absorbed by the blood in the lung. If taken orally, Δ-9-THC is not absorbed into the blood as rapidly. The rate of disappearance of Δ-9-THC from the blood varies with time (Lemberger et al., 1971a,b, 1972; Ohlsson et al., 1980). High blood levels fall rapidly for the first 30 minutes, as the Δ-9-THC distributes to tissues with high blood flow. After the initial distribution, the blood level falls much more slowly with a half-life* of 19 hours or more (Hunt and Jones, 1980). Metabolites† of Δ-9-THC have their own independent rates of elimination. Typically, metabolites are eliminated more slowly, having a half-life of approximately 50 hours (Hunt and Jones, 1980).

After an injection of a single dose of Δ-9-THC, approximately 25-30 percent of the compound and its metabolites remain in the body at 1 week (Lemberger et al., 1971b; Hunt and Jones, 1980). Essentially complete elimination of a single dose may take 30 days or longer (Jones, 1980). Thus, repeated administration of even small doses may lead to an accumulation of drug higher than levels reached at any time after a single dose.

Absorption

Inhaling smoke from a cannabis cigarette or pipe is pharmacokinetically different from ingesting cannabis. Smoking is a far more efficient way of delivering cannabinoids to the brain than ingestion because of the large surface area of the lungs. Inhaled, the cannabinoids in the smoke go rapidly from the lungs into the blood to the left side of the heart and are carried in seconds to the brain and other organs before passing through the liver. When smoked, a drug reaches the brain with relatively little time for metabolism or dilution. Many substances with high lipid solubility such as cannabinoids go quickly from blood into tissues, including brain tissues. Psychological and cardiovascular effects of cannabis are

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*The half-life is a measure of how rapidly a drug is eliminated. It is the time required for the level of a drug to be reduced by one-half. If starting levels are ten units and the half-life is 24 hours, then 1 day after administration, the level will be 5 units, 2 days after administration 2.5 units, etc.

†There are more than 45 metabolites of major cannabinoids identified in different species, at least one of which, 11-OH-Δ-9-THC, is psychoactive.

evident within a few seconds of inhalation. Peak effects occur about the time smoking is completed.

When taken by mouth, cannabinoids usually are in solutions or suspensions. The material they are mixed with affects the rate of absorption. For example, blood levels of Δ-9-THC were higher and lasted longer when given in an oily solution than in an ethyl alcohol solution (Perez-Reyes et al., 1973). This suggests that cannabis eaten in food mixtures containing fat is better absorbed.

An important difference between smoking and ingestion is that when cannabinoids are absorbed from the gut, the blood containing them first goes directly through the liver. The liver rapidly clears the Δ-9-THC from the blood and enzymatically changes much of the Δ-9-THC to other metabolites before it reaches the brain (Hunt and Jones, 1980). A large amount is metabolized to 11-hydroxy-Δ-9-THC (Figure 1). It is unknown if the spectrum of effects of this metabolite is identical to that of Δ-9-THC. When taken by mouth, in contrast to when smoked, two or three times more Δ-9-THC is required to obtain equivalent acute psychological and physiological effects. After oral doses the effects develop more slowly, last longer, are more variable, and cannot be controlled by the recipient once the cannabis has been swallowed. In contrast, the smoker feels the effects quickly and can modify inhalation at any time, although overdosage is still possible. Unpleasant reactions to overdose are more common following ingestion than inhalation.

A variety of other routes of administration have been used experimentally in humans and in animals, including intravenous, intraperitoneal, subcutaneous, intramuscular, topical (on the skin), and into the conjunctival sac (eye). These various routes influence the time to onset of effect, duration and peak intensity, and the rate with which the effect disappears. Direct comparison of findings in studies using differing administration routes is difficult and must take these factors into consideration.

Human users of cannabis vary in their preferred routes of use. In some countries and cultures cannabis is mainly taken by ingestion (for example, India) and in others by inhalation (for example, the United States). Because of the effects of route of administration on pharmacology, it is reasonable to expect different health consequences of the different routes of administration; therefore, comparisons of health statistics among countries must be made with care.

Although smoking avoids many of the absorption problems discussed above, a host of other variables affecting dose are introduced, such as the size and packing of the cannabis cigarettes, the way the smoke is inhaled, the number of puffs and the interval between puffs, the temperature produced in the burning cigarette, and whether a cigarette is shared. Because of the progressive concentration of cannabis constituents in the cigarette butt, the last few puffs yield considerably more Δ-9-THC and particulate matter than do the earlier puffs. All these and other factors affect the dose received, and only rarely have they been measured. Only some of these factors are under the conscious control of the cannabis smoker. About half of the Δ-9-THC originally in a cannabis cigarette is lost by

combustion, by butt entrapment, in smoke not inhaled, and in smoke exhaled (Fehr and Kalant, 1972; Rosenkrantz, 1981).

It has been reported that, like nonsmokers of tobacco, individuals in a poorly ventilated room where cannabis is smoked may passively inhale active components (Zeidenberg et al., 1977). Because only trace amounts of cannabinoid metabolites are present in urine of these passive inhalers, it is unlikely that the low levels of the absorbed cannabinoids from the ambient air account for the so-called "contact high." Experiencing subjective cannabis effects in the presence of cannabis smokers could be explained by psychologic factors in addition to any pharmacologic ones. But, because studies have shown that children of parents who smoke tobacco are more likely to have respiratory infections during the first year of life--which may be due to their being exposed to cigarette smoke in the atmosphere (U.S. Department of Health, Education, and Welfare, 1979)--the issue of passive inhalation of marijuana smoke is worth further study.

Distribution

The lipid solubility of Δ-9-THC and other cannabinoids, including those with highest pharmacologic activity, facilitates distribution readily into tissues and cells throughout the body so blood levels drop rapidly. Initially, cannabinoid concentrations are highest in such tissues as lung, liver, and kidney that have a high blood flow (Agurell et al., 1969, 1970; Klausner and Dingell, 1971). Delta-9-THC crosses the placenta and enters the fetus of experimental animals (Kennedy and Waddell, 1972). Cannabinoid levels in the human fetus have not been studied. Small amounts are also found in the milk of experimental animals and can be transferred to progeny (Jakubovic et al., 1973; Chao et al., 1976). After initial distribution, concentrations of cannabinoids in tissues, cells, and subcellular compartments are highly nonuniform, determined no doubt by solubility and other physicochemical characteristics. Therefore, blood concentrations do not reflect concentrations at pharmacologically active sites, as they do with alcohol.

Metabolism and Elimination

Elimination of drugs and their metabolites is mostly through excretion by the kidney into the urine or by the gall bladder via the bile into the intestine and out with the feces. Cannabinoids do not pass out of the blood into the lungs and do not appear in breath in appreciable quantities. Some cannabinoids going into the intestine with bile are reabsorbed. Some also diffuse back through the kidney tubules during the process of urine formation, so the amounts finally excreted per unit of time are small. The net result of this recycling is that the cannabinoids are only slowly eliminated from the body.

Studies of the disappearance of Δ-9-THC from human plasma have led to reports of values of half-lives that ranged from 19 hours in experienced users (Hunt and Jones, 1980) to 57 hours in naive users (Lemberger et al., 1971b). Whether this difference in half-life is due to the experience of the user has not been established. Because of their high lipid/water partition coefficients, Δ-9-THC and some of its metabolites can be sequestered in fatty tissues. Following the intravenous administration of radioactive Δ-9-THC to human volunteers, however, 67 percent of the radioactivity was excreted in 1 week, 22 percent in the urine and 45 percent in feces (Lemberger et al., 1971a). Almost no Δ-9-THC itself was excreted in the urine. There may be fairly rapid and complete metabolism of free Δ-9-THC followed by slow release and metabolism of sequestered Δ-9-THC and retained metabolites. Because no direct measurements of cannabinoid levels have been made in tissue samples from human cannabis users and the data are limited in experimental animals, one can only infer from blood levels what metabolites are accumulating and where.

In rats, after inhalation or intravenous administration of radioactive Δ-9-THC, radioactivity persisted in the brain for at least 7 days, mostly as metabolites (Ho et al., 1970). When given subcutaneously in rats, even at intervals as great as a day or two apart, Δ-9-THC will accumulate as metabolites (Kreuz and Axelrod, 1973). Accumulation of some cannabinoids with even less frequent intake appears likely. Although most metabolites are concentrated in fatty tissues, they will slowly pass into plasma and circulate though all parts of the body, particularly including such organs as the brain, and generally all membranes. The health consequences of the continued presence of such foreign molecules are not known. The marked persistence of the cannabinoids is quite unlike other widely consumed agents, such as alcohol, nicotine, and caffeine, that are rapidly metabolized and leave no trace a few hours after moderate intake.

WHAT IS A LARGE OR SMALL CANNABIS DOSE?

Large and frequent doses of any drug are more likely to produce adverse health effects than small infrequent doses of the drug. Thus, judgments of health consequences of the use of cannabis can only be made with implicit or explicit knowledge about dose. For the reasons discussed above, the range of cannabinoid doses consumed varies widely. Investigators usually report dose in terms of marijuana cigarettes per unit of time, or they give some estimate of the concentration of Δ-9-THC used for oral application. This is not an adequate way to quantify the amount of cannabinoids actually entering the body. Only one epidemiologic study provides a breakdown of varying dose levels in excess of one cannabis cigarette daily (Bachman et al., 1981). Epidemiologic surveys have not quantified Δ-9-THC levels. When reporting less frequent use patterns than one cigarette per day, investigators use measures that make it difficult to compare studies. In this report, any general or average dose estimates are approximations.

It is generally agreed that smoking five or six 1-gram cannabis cigarettes daily is a large dose (Dornbush et al., 1971; Rosenkrantz, 1981). Because of the variability of Δ-9-THC content of cannabis available from street samples, it would be more appropriate to consider this heavy use. The definition of a low dose is more controversial. Some consider one marijuana cigarette a day to be a large dose. Others think even one cigarette a week is regular, frequent, and a high dose.

With tobacco and alcohol, for which dose is easier to quantify, it took many years to establish what a small or large dose might be in terms of specifying doses that significantly increased the risk of various behavioral and health consequences. Even with those drugs, there is still disagreement as to precisely what a small and "safe" dose might be. There will be even more problems in specifying typical cannabis doses and predicting their likely health consequences.

In controlled laboratory conditions, ingested doses of more than 20 mg of Δ-9-THC generally are considered by both investigators and cannabis users to be large doses. Doses of less than 10 mg are considered small. Marijuana cigarettes containing more than 20 mg of Δ-9-THC seem to be a large dose, and those with 10 mg produce effects generally considered the result of a small dose. When volunteers were allowed to select their own self-determined smoked doses in controlled experiments, some smoked only one or two 20-mg cigarettes daily, while other similar volunteers smoked six to ten or more cigarettes per day. Variability in smoking patterns is great and not easily quantified; only broad range estimates of dose are possible.

GENERAL TOXICOLOGY

Delta-9-THC and related cannabinoids have very low lethal toxicity. That is, a very high single acute dose of Δ-9-THC is required to kill half of a population of experimental animals. This lethal dose for 50 percent of the animals is called the LD_{50}. The lack of well-authenticated cases of human deaths from acute Δ-9-THC or cannabis overdose is consistent with the experimental animal data. The lethal dose increases as the phylogenetic tree is ascended. The rat has an LD_{50} of 40 mg/kg intravenously, in contrast to a 125 mg/kg in the monkey (Rosenkrantz, 1981). Death is usually due to cardiac dysfunction. Delta-9-THC appears to be the most toxic of the cannabinoids.

Studies of chronic cannabis administration to animals have demonstrated delayed lethality. Animals die after several days of a repeated high dose (Rosenkrantz, 1981). The reason for this pattern is unclear. It could be related to accumulation of Δ-9-THC or metabolites in tissues.

A 1-year chronic treatment of rats with lower doses of cannabinoids produced a pattern of toxicity consisting of weight loss, pulmonary pathology when the drug is inhaled, and slowly

developing behavioral toxicity characterized by hyperactivity, vertical jumping, fighting, and seizures (Rosenkrantz, 1981).

RELEVANCE OF NONHUMAN ANIMAL MODELS

Much of what is known about cannabis comes from experiments in animals. Some aspects of the pharmacology of any drug can only be studied in animals other than human beings. Findings from animal experiments have been criticized because of what were thought to be unreasonably high doses of cannabis given to the animals as compared with doses commonly used by human beings. Although extrapolation of human effects from animal data must be done with caution because of species differences in metabolic pathways and differing sensitivity and physiology, a blanket criticism of animal studies because of high doses is inappropriate. When an effect of a drug occurs consistently in several species, it is likely to occur in human beings. Comparisons of Δ-9-THC blood levels in human beings and in several species suggest roughly similar intensity of effects at similar blood levels in the various species (Rosenkrantz and Fleishman, 1979).

CANNABIS CONTAMINANTS

On occasion cannabis has been reported not only to contain the herbicide paraquat, but also salmonella bacteria and aspergillus fungus. Deliberate addition of such drugs as lysergic acid diethylamide (LSD), heroin, and phencyclidine (PCP) has been claimed. A plant material such as cannabis is not always handled in the most sanitary way, and a variety of contaminants are possible.

Paraquat

There is no question that large doses of paraquat by mouth or by aerosol can cause pulmonary fibrosis, but no cases in human beings have yet been proved to result from paraquat-contaminated cannabis. Few cannabis smokers are expected to be exposed to the large amounts of paraquat known to cause severe lung damage. This is not to say that no lung damage will occur from such exposure. A more extensive discussion of paraquat is in Appendix D.

Bacteria and Fungi

A few outbreaks of salmonellosis epidemiologically linked to marijuana use were reported from Ohio and Michigan (Schrader et al., 1981). Marijuana was found to be contaminated with the same type of salmonella that was obtained from the 62 patients experiencing diarrhea, fever, and abdominal pain.

Aspergillus, a fungus, is a common contaminant of some cannabis (Llewellyn and O'Rear, 1977; Llamas et al., 1978). The spores pass easily through contaminated marijuana cigarettes and when smoked are presumed to enter the body.

CELLULAR TOXICITY

A variety of effects on cellular processes have been reported, usually based on studies of in vitro systems. The low water solubility of the cannabinoids and the need to add solvents and emulsifiers, along with a common tendency to use higher in vitro concentrations than occurs in living animals, makes interpretation of such experiments difficult.

In related studies, Δ-9-THC alters the actions of a number of intracellular enzyme systems. The biological relevance of these drug/enzyme interactions is still unclear at this time, but, together with the cytotoxicity, it suggests that Δ-9-THC is producing marked effects on cell membranes and intracellular processes.

Almost nothing is known of the molecular mechanisms by which cannabinoids produce their effects in cells.

TOLERANCE AND DEPENDENCE

Repeated administration of most psychoactive drugs leads to the development of tolerance. This state of increased drug resistance results from two general mechanisms (Kalant et al., 1971):

- Dispositional tolerance resulting from lower drug concentrations at sites of action, usually because of increased rates of drug metabolism or elimination
- Functional tolerance arising from decreased sensitivity of the target cells.

Tolerance to most cannabinoid effects has been demonstrated both in animals and human beings (Jones, 1981). Tolerance can develop rapidly after only a few small doses. It disappears at an equally rapid rate for many effects, although after large doses in experimental animals some tolerance may persist for long periods (Jones, 1981). Systematic studies of tolerance loss have rarely been done. Many characteristics of tolerance to Δ-9-THC, particularly its pattern of rapid acquisition and loss, are similar to that occurring with opiates, nicotine, and cocaine (Jones, 1981). Most evidence suggests functional rather than dispositional means of acquiring tolerance.

The development of such tolerance to cannabis does not necessarily have health implications. However, if tolerance should lead to higher or more frequent doses, adverse consequences, e.g., respiratory effects, associated with higher usage could result.

Physical dependence, manifested by withdrawal signs and symptoms, can develop rapidly in animals and in human beings (Jones, 1981). The withdrawal syndrome is not life threatening. It is similar in many respects to the mild dependence produced by low doses of other sedatives. Withdrawal symptoms can include restlessness, irritability, mild agitation, insomnia, and sleep EEG disturbance.

Cannabis dependence does not mean the same thing as cannabis addiction. Dependence means only that a withdrawal syndrome can occur when drug taking is stopped. Addiction implies compulsive behavior to acquire the drug. The relationship between dependence and increased drug seeking or drug using is more theoretical than well documented, particularly in experiments with human beings. Given the appearance of tolerance and dependence with almost any psychoactive drug, it would be unusual not to find tolerance and dependence with the right dose and dosage schedule of cannabis. Good studies of the relationship of dependence, if any, to persistent drug use are important.

DRUG INTERACTIONS

Because cannabis often is consumed with other drugs, interactions can be expected. Other illicit drugs, tobacco, caffeine, alcohol, and over-the-counter or prescribed medications should be studied in combination with cannabis, because Δ-9-THC and its first metabolite are strongly bound to proteins in the plasma (Garrett and Hunt, 1974) and may interact with other drugs similarly bound. Cannabis and many other drugs share disposition by the hepatic metabolic enzyme systems, and there are possible interactions at the drug metabolism level. For example, drugs such as alcohol or pentobarbital can inhibit metabolism of Δ-9-THC by enzyme substrate competition. Or, if after a period of inhibition one drug is removed, the enzyme activity can increase so that faster than expected metabolism follows. If given simultaneously with other drugs, Δ-9-THC can slow metabolism of drugs such as theophyllin, antipyrine, ethanol, and pentobarbital (Benowitz and Jones, 1977; Jusko, 1979). Cannabidiol can also inhibit the metabolism of a variety of drugs normally metabolized by the shared hepatic enzyme systems.

Drug interactions also can occur by means of functional mechanisms. These can be additive, resulting in enhancement or prolongation of behavioral and psychological effects by cannabis when combined with other central nervous system depressant drugs, such as alcohol and barbiturates. Animals less tolerant to cannabis will also be less sensitive to other central nervous system depressants. This phenomenon is known as cross-tolerance. Drug interactions will be mentioned in subsequent chapters.

SUMMARY AND CONCLUSIONS

Cannabis is not a single drug, but a complex preparation containing many biologically active chemicals. The psychological and physiological effects produced by Δ-9-THC probably result from actions at sites within the central nervous system and elsewhere in the body, leading to the likelihood of complicated effects depending on dose, duration of use, and many other considerations.

The intensity of effect an individual experiences varies considerably according to the cannabis preparation and the amount taken, route of administration, frequency of use, and probably other not-well-recognized biological considerations. Dose variability must be considered both in conducting and in interpreting any studies of the effects of cannabis, particularly when trying to predict health consequences.

In research the use of pure Δ-9-THC avoids some problems of dose control but cannot provide a complete picture of cannabis effects, because the effects of Δ-9-THC in crude preparations of the plant may be influenced by other components. Other consequences of cannabis use, for example, exposure to harmful components in its smoke, will have deleterious health consequences in addition to anything produced by the Δ-9-THC.

The long persistence of cannabinoid metabolites in the body may have delayed effects or health implications not yet recognized, because, even with relatively infrequent use, there is chronic exposure to biologically unknown materials. In this respect, cannabis differs fundamentally from such drugs as alcohol, nicotine, and caffeine, which are rapidly metabolized and eliminated from the entire body.

Cannabinoid effects can be modified by many events, including interaction with other drugs and the development of tolerance. Both tolerance and dependence develop to many effects of the drug. The health significance of tolerance and dependence, particularly their importance in drug-seeking and drug-using behavior, has not been studied properly.

It is unlikely that adequate epidemiologic data will be available (soon) to enable good estimation of the health consequences of various usage levels.

A prerequisite is that adequate chemical analytical methods be applied on a large-scale basis to monitor actual exposures. Continued studies in experimental animals will play an essential role in the assessment of the health risks of cannabis. For example, the biological activities of Δ-9-THC metabolites can be assessed in experimental animals, but these tests are technically more difficult to do in human beings.

RECOMMENDATIONS FOR RESEARCH

Several research priorities are identified by the preceding discussion:

• Cannabinoids and their metabolites persist for relatively long periods in the body. More information is needed on the biological significance of that persistence in human beings. As a first step, the toxicological effects of the various metabolites need to be determined.

• Drug interactions alter the actions of cannabis. Cannabis use alters other drug effects. More information is necessary to make the combined effects of cannabis and other licit and illicit drugs more predictable, especially with respect to behavioral impairment and toxicity to lungs, liver, and other organs.

• Studies of the mechanism of action of cannabis should continue. Knowledge of mechanism is likely to provide powerful insights into the potential health effects.

• Improved chemical analytical methods are necessary. Epidemiologic appraisal of the health effects of cannabinoids requires methods suitable for wide-scale assays of exposures. Pharmacological verification of the self-reported extent of use will make experimental and clinical results much easier to interpret. A chemical "marker" of the frequent user would be useful. Screening techniques for the purpose of identifying and discouraging cannabis-impaired driving would also be valuable.

• Characterization of the toxicological significance of common cannabis contaminants such as paraquat and other chemicals, fungi, and bacteria should be continued.

• The development of tolerance is a factor that potentially modifies the expression of all psychoactive drug effects. Additional studies on the rates of acquisition and loss of tolerance and the relationship of these phenomena to dependence are necessary. The biological significance of the changes that underlie the development of tolerance should be established. The relationship, if any, between tolerance and dependence and drug-seeking behavior should be established.

• Cannabis products are variable and complex. More information on the amount, nature, and potency of the various preparations used around the world would facilitate calculations of exposures to its constituents. For example, what is the biological and toxicological significance of the minor components of cannabis smoke?

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USE OF MARIJUANA IN THE UNITED STATES

Epidemiologic studies provide information on the use of drugs in various subgroups of the population and on the changes in patterns of use over time. The epidemiologic approach is particularly useful in defining patterns of use of marijuana in American society and in describing and analyzing the behavioral and psychosocial antecedents and consequences of that use. One of the more difficult questions is whether particular behavior or effects that are associated with use of a drug are the consequences of that use, or whether attitudes, values, and behavior develop about the use of drugs to constitute factors that may actually lead to the use of drugs. One of the more useful epidemiologic study designs is a cohort study that follows the same individual with repeated observations at regular intervals over time. Such longitudinal studies have the potential for obtaining the most compelling evidence on the antecedents of known patterns of use of marijuana, as well as possible long-term psychosocial and biological outcomes for these individuals.

The committee, with the help of consultants, sought answers in the epidemiologic literature to the following five questions:

1. What are important patterns of use of marijuana in the American population including special groups?
2. What are the general characteristics of users of marijuana?
3. What is the profile of a user of marijuana on a "daily"* basis?
4. What is known about the antecedents of use of marijuana?
5. How is use of marijuana related to the use of other drugs?

The epidemiologic and survey literature have been extensively reviewed and the major longitudinal studies are summarized in a table in Appendix C. Much of our recent knowledge derives from two well-designed major, continuing nationwide monitoring efforts

*When placed in quotation marks, "daily" is used as defined by Johnston et al. (1980b), i.e., those individuals using marijuana 20 or more times in the preceding 30 days.

sponsored by the National Institute on Drug Abuse. One is based on general household population samples, the National Household Surveys. The second is based on populations of high school seniors and is called Monitoring the Future.

The National Household Surveys of the general population are conducted on an annual or biannual basis by Response Analysis Corporation and The George Washington University (Fishburne et al., 1980). There have been six cross-sectional studies since 1971. The latest one was in the winter of 1979-1980, and the next one will be initiated in 1982. The subjects are classified as youth (12-17), young adults (18-25), and older adults (26 and older). The questions relate to marijuana and other psychoactive drugs, including inhalants, hallucinogens, cocaine, heroin, stimulants, sedatives, and analgesics. Samples vary from about 3,000 to more than 7,200 new respondents at each survey. These are samples that document patterns of use of drugs in the specified populations at a given time.

Monitoring the Future (Johnston et al., 1980b) uses a cohort-sequential longitudinal design, in which a new cohort of high school seniors is surveyed each year, and a representative panel selected from that senior class is also followed over time in successive annual or biannual testings. The earliest panel has now been reinterviewed six times. This survey design makes it possible to disentangle antecedents from consequences of use as well as to distinguish changes due to increased age from changes due to cohort peculiarities or historical circumstances. Initiated in 1975 by the Survey Research Center of the University of Michigan, and directed by Lloyd Johnston and Jerald Bachman, the survey involves a questionnaire self-administered each year by more than 16,000 high school seniors in 130 public and private schools throughout the United States, and longitudinal mail follow-ups of about 2,000 former students drawn, as panels, from each of the previously participating senior classes (Johnston et al., 1979a,b; 1980a,b).

Because the National Household Surveys and Monitoring the Future are surveys of persons in households or in high school, they exclude persons most likely to be using drugs--the transients, those without regular addresses, the school absentees or drop-outs, or those living in institutions or group quarters. These persons constitute a small proportion of the general population, and their exclusion does not significantly bias the epidemiologic estimates reported for the total population (Kandel, 1975a). However, data on the very heavy use of drugs may be underrepresented.

PATTERNS AND TRENDS OF USE OF MARIJUANA

General Population

The National Household Surveys found that marijuana was the most commonly used of all the nonlegal psychoactive drugs investigated, including inhalants, hallucinogens, cocaine, heroin, stimulants, sedatives, tranquilizers, and analgesics (Fishburne et al., 1980).

In 1979 more than 50 million persons had tried marijuana at least once in their lives: 68.2 percent of young adults (18-25), or about 21 million; 30.9 percent of youth (12-17), or more than 7 million; and 19.6 percent of older adults (26 and older), or 25 million. The young adult age-group (18-25 years) has consistently showed the highest rates of current use (used in past month) and ever use (lifetime prevalence), and the older adult groups (26 and older) had the lowest user rates. Male users outnumbered females in all age groups. Between 1977 and 1979, significant increases in current use and ever use of marijuana were observed among the young adult and older adult cohorts (Figure 2). In 1979, in the young adult cohort, the most significant increases in use in the past month were found in males, whites, high school nongraduates, people in the southern United States, and those living in nonmetropolitan areas. In the older adult groups, the most significant recent increase in current use of marijuana was observed in males, whites, college graduates, and people living in the southern states (Miller and Cisin, 1980).

In the early 1960s, illicit drug use in the United States was chiefly a phenomenon of large coastal cities. But since then, rates in other regions of the country and in cities of all sizes have rapidly increased until patterns of use are becoming increasingly comparable for all sectors in the United States. At current levels of use, some experience with marijuana in adolescence is becoming the norm rather than the exception throughout the United States. Other major survey studies have confirmed the findings of the National Household Survey for comparable cohort populations (Gallup Opinion Index, 1976; O'Donnell et al., 1976).

Military Personnel

Much attention has recently been focused on what appear to be high rates of use of illicit drugs among military personnel. Studies of drug use among male army veterans of the Vietnam War in 1972 showed that marijuana was the most commonly used illicit drug before and after the war (Robins, 1974). A random sample of 470 men was selected from the 13,760 enlisted men who returned to the U.S. in September 1971. Of the 451 men who were interviewed, 69 percent had used marijuana while in Vietnam, with 28 percent stating this was their first use of the drug. The lifetime prevalence of use of marijuana was 41 percent prior to Vietnam; 45 percent of the veterans reported using marijuana in the 10 months following return to the United States. Among this group the prevalence of weekly use doubled from 12 percent prior to Vietnam to 25 percent following the war.

A worldwide survey of nonmedical use of drugs and alcohol among U.S. active duty military personnel was conducted in 1980 under the sponsorship of the U.S. Department of Defense (Burt et al., 1980). In an anonymous, self-administered questionnaire given to a representative sample of more than 16,000 persons, marijuana was found to be the most commonly used illicit drug. Twenty-six percent admitted to having used "marijuana/hashish" within the past 30 days and 35

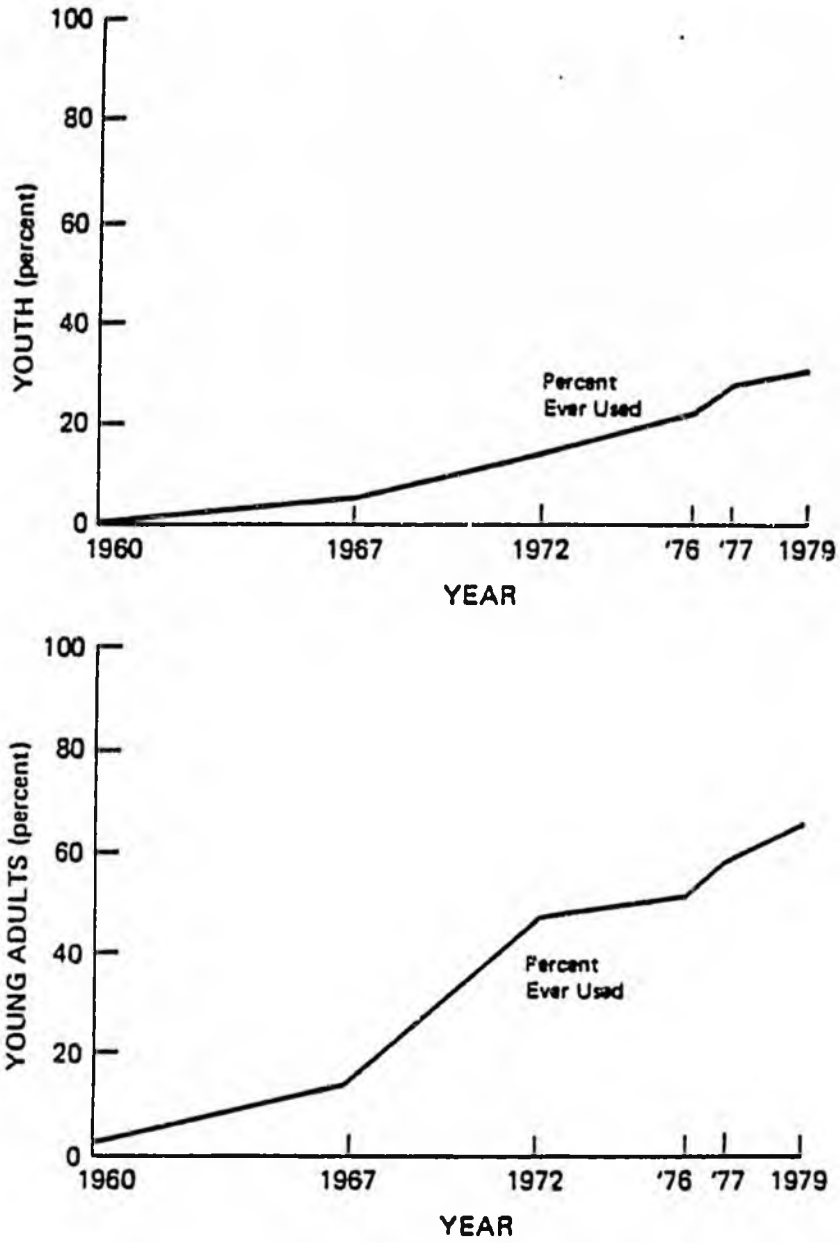


FIGURE 2 Marijuana: trends in lifetime experience, youth, and young adults. Adapted from J.D. Miller and I.B. Cisin. Highlights from the National Survey on Drug Abuse: 1979. Washington, D.C.: U.S. Government Printing Office, 1980. Youth = 12 to 17 years old; young adults = 18 to 25 years old.

percent to having used it in the past 12 months. Five percent of the sample reported use of marijuana daily.

When users of drugs were itemized according to military pay classifications, the largest percentage of current use of marijuana was in the lowest ranks of the military.

Adolescents and Young Adults

Patterns and Trends

One of the compelling reasons to focus on adolescence in studying marijuana is the pervasive and increasing use by this age group. As was mentioned earlier, in 1980 all geographical regions of the United States and all socioeconomic classes had high and increasingly comparable involvement in use of marijuana.

The year 1960 has been taken as a baseline year that represents the stable level of overall use of marijuana that had characterized the United States for most of its history. Figure 2 shows the trends for use of marijuana from 1960 through 1979, revealing the sharp upward climb of use of marijuana starting in 1967. The dramatic rise in use of marijuana by adolescents has recently slowed, and the lifetime prevalence rates (ever use) of marijuana have remained at approximately 60 percent of all high school seniors for the years 1979 and 1980 (Figure 3). To put it another way, in 1979 over 2.5 million high school seniors had tried or were users of marijuana. (This figure is derived from calculations based on 1979 Census Bureau data that give a figure of 4,276,000 for number of 18-year-olds in the population. The committee is aware that all 18-year-olds are not high school seniors and that such a calculation may underreport the numbers of users of marijuana, particularly heavy users who have been shown to be more likely to have dropped out of school. Similar calculations have been attempted throughout this chapter.)

The use of other types of drugs by young people also increased beginning in 1967 (Miller and Cisin, 1980). Figure 4 gives the most recent nationwide figures for use of 11 types of drugs among American high school seniors (average age 18 years). With the exception of negligible use of heroin, the figures for use of all other drugs are substantial. Increases in patterns of use have not been as dramatic for other drugs (except for recent cocaine increases) as they have been for marijuana. Use of marijuana, tobacco, and alcohol far outstrips that of all other drugs. In 1980 the lifetime prevalence (ever use) for these substances by high school seniors was marijuana--60 percent, tobacco--71 percent, and alcohol--93 percent.

Of even greater interest are the percentages of high school seniors who use the 11 types of drugs "daily." In 1980 marijuana was used "daily" by 9.1 percent (about 390,000), alcohol by 6.0 percent (about 256,000), and tobacco cigarettes by 21.3 percent (about 900,000) of high school seniors (Johnston et al., 1980a). No other substance was used that frequently by as many as 1 percent of the

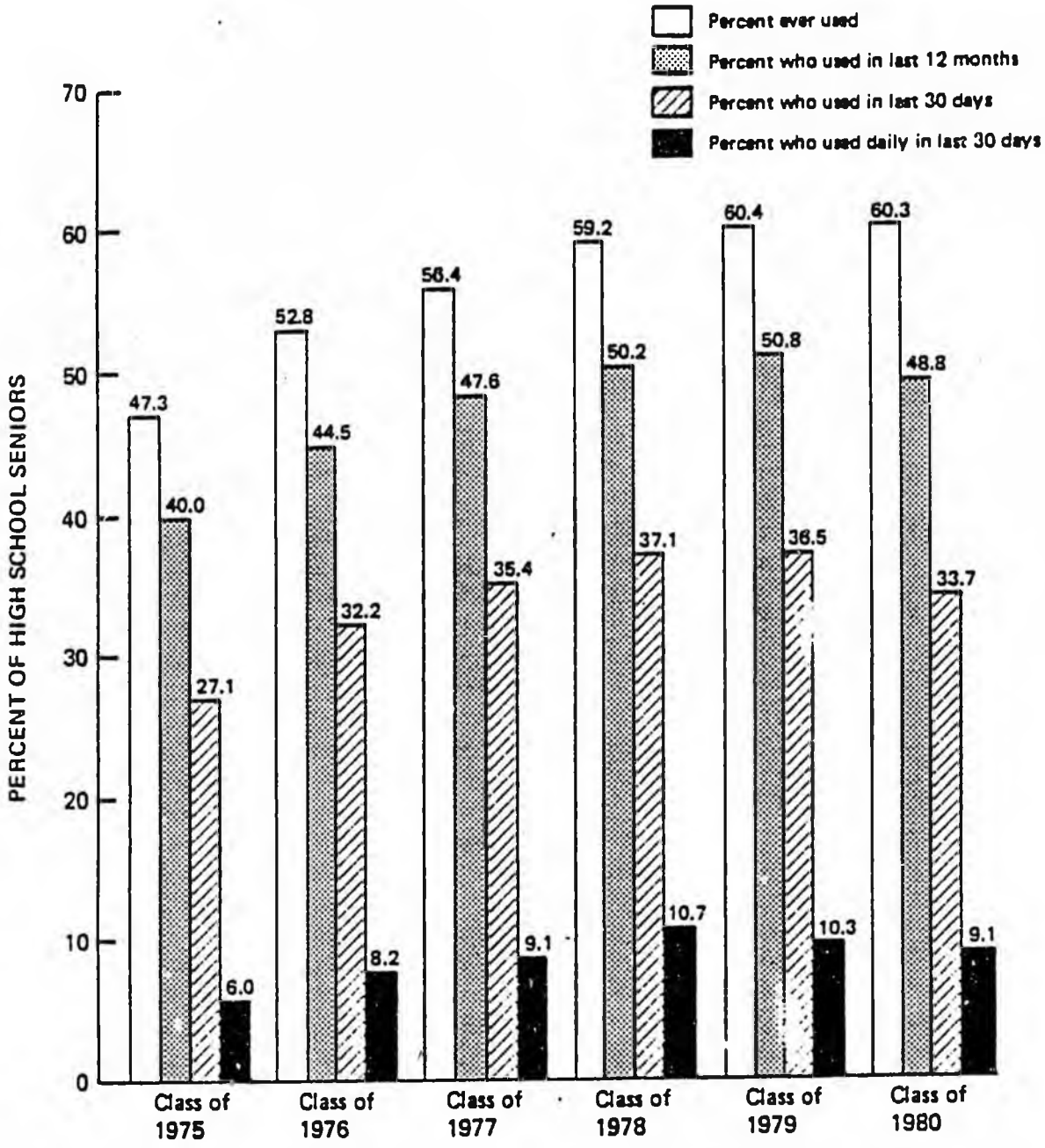
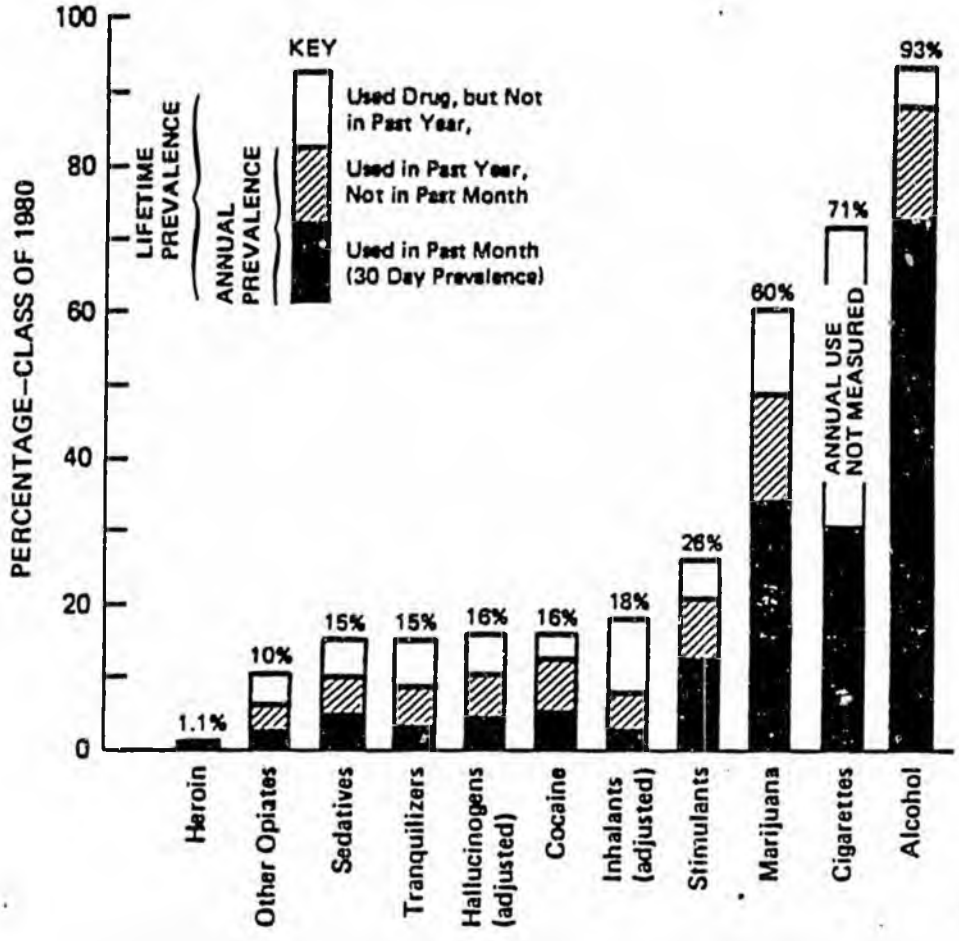


FIGURE 3 Trends in prevalence of marijuana use by high school seniors, 1975-1980 (in school). Adapted from L.D. Johnson, J.G. Bachman, and P.M. O'Malley, Highlights from Student Drug Use in America, 1975-1980. DHHS Publication No. (ADM) 81-1066. Washington, D.C.: U.S. Government Printing Office, 1980a.



NOTE: The bracket near the top of a bar indicates the lower and upper limits of the 95% confidence interval.

FIGURE 4 Prevalence and recency of use. Eleven types of drugs, class of 1980. SOURCE: Johnson, L.D., Bachman, J.G., and O'Malley, P.M. Highlights from Student Drug Use in America, 1975-1980. DHHS Publication No. (ADM) 81-1066. Washington, D.C.: U.S. Government Printing Office, 1980a.

students. These figures show that legal (for adults) drugs are used much more frequently than illegal ones. Reports of illegal use of drugs show that experimentation with marijuana has, by far, the highest prevalence. It should be noted, also, that "daily" use of marijuana (9 percent) among high school seniors is now more prevalent than "daily" drinking (6 percent) of alcoholic beverages.

In 1980, for the first time since 1975, when the Monitoring the Future data collection began among high school seniors, the percentage of "daily" users of marijuana among seniors in high school declined significantly from 10.3 percent in 1979 to 9.1 percent in 1980 (Figure 3), and there was a leveling of lifetime prevalence at approximately 60 percent. Furthermore, the proportion of current users among those who ever used marijuana also showed a statistically significant decline in 1980 as compared to 1979, from 60 percent to 56 percent. However, "daily" users may be increasingly underrepre-

sented in recent senior high school classes due to absenteeism and drop-out associated with increasingly earlier and extensive involvement in use of marijuana. The extent to which long-term "daily" users have dropped out of school by the senior year of high school cannot be ascertained from monitoring the future. Kandel (1975a) found that absentees differed from students attending school regularly. Fifty-six percent of absentees reported use of marijuana as compared to 38 percent of in-class students. Studies that document the patterns of marijuana use in school drop-outs are needed.

Correlates of Use

Overall levels of use of marijuana have been shown to correlate with patterns of use of the drug.

1. Increased prevalance is associated with younger age of initiation into use of marijuana. As successive cohorts of high school seniors have shown increasingly higher levels of experience with marijuana from 1975 through 1980, these cohorts also report increasingly earlier ages at first use of marijuana. For example, in the senior class of 1980, which had a lifetime prevalence of 60 percent by senior year, 25 percent of those using marijuana had begun in the eighth grade (average age 14) or below. In 1975 when lifetime prevalence was 47 percent, 15.3 percent of marijuana users had begun in eighth grade or below. It is of some interest to compare reported age of use of marijuana by grade for the senior class of 1980 (lifetime prevalence 60 percent) and alcohol (lifetime prevalence 93.2 percent). The more prevalent drug, alcohol, is used at earlier ages than marijuana. Thirty-three percent of alcohol users had started at eighth grade as compared to 21.5 percent of marijuana users (Johnston et al., 1980a).
2. Earlier onset of use of any drug is associated with greater involvement in use of all other drugs. The earlier the introduction to legal (for adults) drugs, the greater the probability that the adolescent will also experiment with illicit drugs. For example, among young adults 18-25 years of age surveyed from the general population in 1979-1980, the proportion who had experimented with any illicit drug other than marijuana ranged from 87 percent among those who reported having first tried alcohol or marijuana at ages 13 or 14, to 47 percent among those who first tried these drugs at ages 15-17, and 5 percent among those who first experimented at age 18 or over (Rittenhouse, 1980). The finding that the earlier the experimentation with marijuana, the greater the intensity of involvement and the greater the likelihood of using more serious drugs has been confirmed in many studies (e.g., Miller and Cisin, 1980; Johnston et al., 1980a; Kandel et al., 1981).
3. Greater overall prevalence of use of marijuana is associated with greater persistence of use of marijuana into later years of adult life. The current prevalence rates for use of marijuana by persons in their mid-30s are increasing (Cisin et al., 1978). Many

studies have not sampled this population in the belief that use of marijuana drops off sharply in the mid-20s. Among males, the prevalence rate for use of marijuana in the past month for over-26-year olds went from 4 percent in 1977 to 9 percent in 1979. It will be exceedingly important to monitor the trends in all older adult age groups.

Marijuana and the Use of Other Drugs

One of the key questions asked over the years is, does marijuana lead to the use of other drugs. In any population, the use of various drugs appears interrelated and users of any type of drug, whether legal or illegal, are much more likely to use other types of drugs than nonusers. For example, young people who smoke tobacco are also much more likely to have used alcohol or marijuana than nonsmokers (Fishburne et al., 1980). Similarly, there is a strong association between the use of marijuana and of other illicit drugs. Young people who use marijuana are more likely to be consuming other substances, such as alcohol and tobacco, as well as other illicit drugs (Johnston et al., 1980b). The association increases with extent of marijuana involvement and is especially striking among those young people who use marijuana on a "daily" basis, as will be discussed below.

Results from the National Household Surveys and from samples of high school seniors had indicated that the ratio of rates of use of illicit drugs other than marijuana to use of marijuana declined through 1979 (Kandel, 1980; Miller and Cisin, 1980). In 1980, however, the ratio started to rise again. Thus, in 1980, 65 percent of marijuana users among the high school seniors had also used other illicit drugs as compared to 61 percent in 1979 (Johnston et al., 1980a).

"Daily" Users in High School

Because any health risks resulting from the use of marijuana would be most likely to appear first in chronic users of the drug, the young persons who are chronic and heavy users are of special interest. The committee reports in some detail the findings on this group. The ranks of "daily" users are large. In 1980 they represented more than 9 percent of high school seniors or over 390,000 18-year-olds in the United States. One out of 11 seniors fitted the definition of "daily" users (20 or more occasions of reported use within the preceding 30 days). Collection of systematic data on such users began in 1975 with the annual monitoring of in-school high school seniors. There are many gaps in our knowledge about this group, but sufficient data have been accumulated that it is now possible to describe many of the behavioral attributes of the "daily" users. Most of these data come from Monitoring the Future. Some of the findings recently reported by Johnston (1980, 1981) and Bachman et al. (1981) are as follows:

Demographic Findings

Rates of "daily" use do not vary among regions of the country, but "daily" use shows a strong positive relationship to the size of the community and is more prevalent in urban areas. Males are "daily" users at almost double the rate of females (13 percent versus 7 percent). "Daily" use among white students is double that for blacks (11 percent versus 5 percent). "Daily" use is spread evenly across socioeconomic levels as defined in terms of parents' education. "Daily" use is only slightly higher among those from homes in which one or both parents are absent.

Academic Performance and Goals

"Daily" use is associated with poor school achievement. Among non-college-bound seniors the rate of "daily" use is almost double that found among the college-bound (13 percent versus 7 percent). There are strong and positive correlations of "daily" use and cutting classes, school absences, and truancy.

Much of "daily" use takes place within the school setting. A statewide study of seventh through twelfth grade pupils in New York, conducted in 1978 by the New York State Drug Abuse Commission, found that 50 percent of those using marijuana within the last 6 months had been intoxicated one or more times while in class (Johnson and Uppal, 1980). In contrast, alcohol tends to be used most frequently after school and on weekends.

Religious Commitment

A commitment to religion and self-ratings of strong belief in law-abiding behavior are associated with lower than average rates of "daily" use.

Dating and Social Life

Dating and social life show strong relationships with "daily" use of marijuana. Those who spend more time on dates have the highest rates of "daily" use of marijuana. Among those students who go out 6 or 7 nights a week and are practically never at home, 34 percent are "daily" marijuana users.

Use of Other Drugs

"Daily" marijuana users are much more likely than their peers to be extensive users of other drugs. Thus, of seniors in the class of 1979, 27 percent of "daily" users of marijuana drank alcohol as frequently, versus 7 percent for the age-group as a whole; and 59

percent of "daily" users of marijuana smoked cigarettes as frequently versus 25 percent for the group as a whole (Johnston et al., 1980b).

With respect to use of other illicit drugs, the rates for "daily" users of marijuana generally run five to seven times the average for the age group as a whole; 47 percent of "daily" users are current* users of amphetamines; 31 percent of cocaine; and their current usage figures run from 15 to 17 percent for barbiturates, for lysergic acid diethylamide (LSD), for phencyclidine (PCP), for methaqualone, and for tranquilizers. Since nearly two-thirds of daily marijuana users (64 percent) are current users of hashish, they have substantial exposure to a hi -potency form of marijuana.

We also know from data on age at first use that many of these "daily" marijuana users began their use of cigarettes, alcohol, and various other illicit drugs at quite an early age. To illustrate, by the end of eighth grade 40 percent of them had smoked cigarettes "daily" and 50 percent had taken their first drink. Just about half of them (48 percent) first tried marijuana by the eighth grade, and most of the remainder (another 30 percent) started in ninth grade. These are very early ages of initiation for all three drugs. Similarly, these youngsters tend to take up the other illicit drugs at an earlier than average age--though most of that use still is initiated after ninth grade. "Daily" use tends to persist longer into adult life than anticipated. In 1979, 4 years after graduation from high school, 51 percent of marijuana users of the senior class of 1975 were still "daily" users and an additional 34 percent were current although not "daily" users (Johnston, 1980).

"Daily" Users After High School

Using a national sample of 19- to 22-year-olds derived from the follow-up surveys of Monitoring the Future, Johnston (1981) reported on "daily" use of marijuana after high school. (These findings are reproduced nearly verbatim below.)

College Student Status

Student status after high school correlates negatively with "daily" use; that is, full-time college students have the lowest rate (8 percent), part-time students the next lowest (10 percent), and nonstudents the highest rate (13 percent). However, although full-time students have a lower than average rate of "daily" use, they showed the greatest increase after high school (up from 4.5 to 8.3 percent): they simply started from a very low level and in a sense were "catching up."

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*A current user is one who has used the drug in the thirty days preceding the surveys.

Living Status

Young people who are living away from home have a higher proportion of "daily" use than those still living with their parents (12 percent versus 10 percent), probably reflecting the result of reduced social control by parents. Those who remained living with their parents (nearly half) showed relatively little increase in use (up 1.3 percent), while those who moved out increased their daily use rate substantially (up 3.9 percent).

Marital Status

Those who are single are almost twice as likely to be "daily" users as those who are married (11.4 percent versus 6.6 percent), and those without children are somewhat more likely to use marijuana than those with children (11 percent versus 8 percent). It appears that these role responsibilities have a dampening effect on use. In the face of an overall 2.6 percent increase in "daily" prevalence after high school for the whole sample, those who were married showed virtually no increase (up 0.2 percent) and those with children actually had a decline in use (down 1.5 percent).

Type of dwelling

"Daily" use is highest for those living in a rented room (14 percent) or apartment (12 percent), and lowest for those living in a college dorm (8 percent). Obviously one's dwelling arrangement is highly correlated with his or her major activity after high school, as these differences reflect.

Employment

Employment status is unrelated to "daily" use. For those in military service, "daily" use dropped slightly after high school (from 13.4 percent to 12.4 percent). The activity group with by far the lowest "daily" use rate are the full-time homemakers (4 percent), which certainly occurs, in part, because they nearly all are female, married, and in many cases have young children.

Reasons for Using or Abstaining

Reasons for "Daily" Use of Marijuana

What reasons do "daily" users give for their use of marijuana? They tend to use marijuana to produce an intoxicated feeling, to cope psychologically with feelings of distress, to augment the effects of other drugs, and to participate in drug-using friendships. On a

checklist of 13 possible reasons, nearly all of the seniors who were "daily" users checked "to feel good or get high" (94 percent) and "to have a good time with my friends" (79 percent). Two-thirds said they used it to relax (67 percent) and nearly half said they used it to relieve boredom (45 percent). Roughly a quarter of the "daily" users checked each of the following: "to get away from my problems" (27 percent), "because of anger or frustration" (23 percent), and "to get through the day" (22 percent). These psychological coping motives in particular seem to distinguish the "daily" users from the less frequent users. A fairly high proportion (30 percent) also said that they used marijuana to increase the effects of other drugs, while only 10 percent of the other current users gave this reason. Only 11 percent of the "daily" users, or 1 percent of the total sample, stated that they used it because they felt "hooked" or had to have it. All of these responses for seniors were closely replicated among the "daily" users in the 19- to 22-year-old sample (Johnston, 1981).

Nearly all "daily" users (over 85 percent), whether in high school or past high school, say (1) that most or all of their friends smoke marijuana, (2) that most or all of their friends drink alcohol, (3) that more than a few of their friends get drunk every week, (4) that more than a few of their friends smoke cigarettes, and (5) that at least a few of their friends use a number of other illicit drugs. This degree of immersion in a drug-using friendship circle contrasts sharply to what we observe for their peers, even those who are current but less frequent users of marijuana. Clearly the social supports and the social pressures are there, both during and after high school, for the "daily" user to continue his or her habit.

Reasons for Quitting and Abstaining

A number of users of marijuana stop using the drug (Johnston, 1981). Among students (in the classes of 1978 through 1980 combined), those who have used marijuana 40 or more times but have stopped by their senior year give as their most commonly mentioned reason on a comprehensive list of 17 reasons that "they don't feel like getting high" (56 percent mentioned). Also frequently mentioned, however, are concerns about possible physical effects (41 percent); concern about possible psychological effects (38 percent); and, more specifically, concern about loss of energy or ambition (41 percent). These reasons also ranked high among those young people who smoked less than 40 times before they stopped, as did two additional reasons--concern about parental disapproval and finding that use of marijuana was not intrinsically enjoyable.

Concern about possible health effects appears to play a role in young people's giving up the drug and is mentioned considerably more often among quitters now than in 1976. Concern about physical health increased substantially between 1976 and 1980 among all high school seniors, from 35 percent to 57 percent, while concern about psychological damage went from 34 percent to 53 percent. A similar analysis of the reasons given for abstaining by the minority (about

40 percent) of seniors who have never tried marijuana reveals concern about physical (71 percent) and psychological (68 percent) consequences, which are mentioned far more often than any other type of reason. Social or ideological constraints or disinterest in getting high are infrequently mentioned. There also has been a significant increase in health concerns among the abstaining segment since 1976, though not as large as among quitters.

In summary, many "daily" users themselves see some negative consequences of their habit, and there perhaps are some consequences of which they are unaware. The fact that the "daily" smoking of marijuana is proving to be more enduring and stable than many may have thought increases the probability of cumulative, long-term effects. The fact that so many young people are becoming "daily" users now puts a substantial number of people at risk of whatever the long-term consequences may prove to be.

Sequence of Drug Use

Regardless of the age of onset, there is a predictable sequence in the patterns of initiation into the use of available drugs. Independent longitudinal studies have confirmed and identified a stable sequence of drug use (Hamburg et al., 1975; Kandel, 1975b; Kandel and Faust, 1975). The legal drugs for adults, such as alcohol and tobacco, are an early, integral, and crucial part of the sequence. Their use precedes the use of all illicit drugs. At least four distinct successive stages of adolescent involvement with drugs can be identified: (1) use of beer or wine, (2) use of tobacco cigarettes or hard liquor, (3) use of marijuana, and (4) use of other illicit drugs (Kandel, 1975b). A fifth stage, problem drinking, may take place between marijuana and other illicit drugs (Jessor et al., 1980). Adolescents rarely proceed from beer and wine to illicit drugs without use of either hard liquor or tobacco cigarettes as an intermediate step. Furthermore, there is an additive effect such that the highest proportion of adolescents who move to marijuana are those who have experience with both hard liquor and tobacco. For example, among 12- to 17-year-olds in the general population, the proportion who have ever experimented with marijuana is 81 percent among current tobacco cigarette smokers as compared to 24 percent among nonsmokers (Fishburne et al., 1980). However, position on a particular point in the sequence does not indicate that the young person will necessarily progress to other drugs higher up in the sequence. Participation in each stage is a necessary but not sufficient condition for participation in a later stage. There is no evidence to support the belief that the use of one drug will inevitably lead to use of any other drug. In other words, persons at the top of the ladder of use of drugs typically will have used all substances at lower levels, including marijuana. However, those at lower rungs may stay there and not move to higher rungs of the ladder.

For example, data from the National Household Surveys (Fishburne et al., 1980) indicate that of those 18-25 years old who have tried

marijuana, almost all are users of tobacco or alcohol; however, only slightly more than one-fourth of this 18- to 25-year-old population report having gone on to try any illegal drug other than marijuana. Of those who try other illegal drugs, only a very small percentage report being current users (Fishburne et al., 1980).

Although it is of great interest, relatively little is known about the factors that determine which persons will choose to go through the sequence of drug use or the rapidity with which they will do so. Existing research gives us some clues that users of illicit drugs possess some distinguishing features.

There are four clusters of variables--parental influences, peer influences, adolescent involvement in deviant behaviors, and adolescent beliefs and values--that assume differential importance for predicting involvement at each stage of drug behavior (Kandel et al., 1978a,b).

Involvement with drugs legal for adults is the earliest level of drug use. Adolescents who start to drink are exposed to peers and parents who drink, suggesting that these youths learn drinking patterns from their parents. Adolescents who have engaged in a number of delinquent or deviant activities, and who seek high levels of sociability with their peers are likely to become involved with alcohol. Similar patterns are found with tobacco smoking, also one of the earliest drugs to be tried.

The use of marijuana follows that of alcohol and tobacco. It is preceded by acceptance of a cluster of beliefs and values that often reflect disavowal of many standards upheld by adults. Involvement in a marijuana-using peer environment strongly predisposes to its use and is the best predictor (Becker, 1953; Goode, 1970). Participation in minor forms of deviant behaviors, such as those that also precede the use of hard liquor, is also an important precursor.

Antecedents of Adolescent Use of Marijuana

When use of marijuana first came under research scrutiny in the late 1960s, very few youths had experimented with illicit drugs. Much was made of the deviant status of use of marijuana and of the counter-cultural and rebellious meaning that came to be attached to using the drug (Suchman, 1968). Yet even today, when over 60 percent of all high school seniors have used marijuana, those youths who use marijuana are quite different from nonusers. The marijuana users in 1979 show the same patterns of disaffection from major institutions that characterized the users in 1967. The most recent data show that marijuana users perform more poorly in school, are less religious, have performed more delinquent acts, are in trouble with the law, have more traffic accidents, and use more illicit drugs than nonusers. Those persons who also use several illicit drugs show the highest involvement in deviant behaviors. There is a linear relationship with degree of involvement with illicit drugs, such that persons using marijuana exclusively are only quantitatively different from those who have also used harder drugs (Johnston et al., 1980b).

In two cross-sectional national samples of high school students, surveyed in 1974 and 1978, Jessor et al. have found that not only are the patterns of association between use of marijuana and deviant characteristics similar in both surveys, but also that the strength of the associations, as reflected in the sizes of the correlation coefficients, are almost identical. The very same conclusions derive from analyses based on five successive cohorts of high school seniors, sampled at yearly intervals in Monitoring the Future (Bachman et al., 1981).

Longitudinal studies of students aged 12-21 have done much to extend our understanding of the precursors of using various forms of drugs. Studies have been reviewed in detail by Kandel (1978a,b; 1980a; also see Appendix C) and document that many of the factors found to be associated with use of drugs at one point in time, such as low academic performance, crime, low self-esteem, depressive mood, rebelliousness, and other personality characteristics, precede the use of drugs (see in particular Mellinger et al., 1976; Jessor and Jessor, 1977; Johnston et al., 1978; Kandel, 1978a; Kandel et al., 1978b,c; Kaplan and Pokorny, 1978; Smith and Fogg, 1978; Wingard et al., 1979; Kaplan, 1980). Some of the predictive factors can be identified in childhood, such as aggressiveness with or without association with shyness (Kellam et al., 1980, in press) and rebelliousness (Smith and Fogg, 1978).

Other longitudinal studies also document that many of the factors found to be associated with use of drugs at one point in time, such as low academic performance, delinquency, low self-esteem, and depressive mood actually precede the use of drugs (O'Malley, 1975; Mellinger et al., 1976; Jessor and Jessor, 1977; Johnston et al., 1978; Kandel et al., 1978a; Kaplan and Pokorny, 1978; Wingard et al., 1979; Kaplan, 1980).

One study shows not only that certain behaviors predict use of marijuana, but also that drugs may aggravate or exaggerate certain behaviors. A cohort of high school students was followed at annual intervals throughout the four years of high school (Jessor and Jessor, 1977). During this time annual scores for various attributes were charted in four groups of students distinguished by differing drug histories: veteran users, who used drugs pre-high school; early initiates, who began relatively early in their high school career, i.e., between the first and second year of testing; late initiates, who began relatively late, i.e., between the second and the third year; and nonusers, who had not started to use marijuana at the last testing in the senior year of high school (Jessor and Jessor, 1977, 1978). These four groups of students differed on measures, such as general deviant behavior (a 12-item scale measuring frequency of involvement in stealing, fighting, property destruction, truancy, or other delinquent activities in the last year) or value on academic achievement (a five-item scale, measuring the value placed on the attainment of success in school work), at the beginning of the study. Scores predicted if and when students initiated use of marijuana. Those students already involved in use of drugs before high school scored highest on deviance and lowest on achievement motivation at

initial testing and throughout subsequent retests. The scores of all groups of users converged over time so that all three groups increased in deviance scores and decreased in their achievement orientation over the four years. The sharpest changes in scores occurred in the year preceding the drug use.

Peer Influences

The most consistent and reproducible finding in drug research is the strong relationship between an individual's drug behavior and the concurrent use of drugs by his friends. The relationship is stronger when based on adolescents' perceptions of the friends' behavior than on the friends' self-reports (Goode, 1970; Johnson, 1973; Kandel, 1973; Goldstein, 1975; O'Donnell et al., 1976; Brook et al., 1977; Jessor and Jessor, 1977; Kandel et al., 1978a; Orcutt, 1978; Smart et al., 1978; Huba et al., 1979). On no other characteristic except age and sex is the similarity within adolescent friendship pairs as high as it is for use of marijuana (Kandel, 1978c). Such similarity results not only from socialization, the influence of one friend on the other, but also from a process of interpersonal selection (assortive pairing), in which adolescents with similar values and behavior seek each other out as friends. Longitudinal data on the formation and dissolution of friendships indicate that selection and socialization contribute about equally to the similarity in values and behaviors (Kandel, 1978d). Available data on sex differences in peer influence indicate that females are more susceptible than males to such influence (Jessor et al., 1973; Margulies et al., 1977). Susceptibility to peer influence is related to involvement in peer-related activities, e.g., dating or getting together with friends, and to degree of attachment to and reliance on peers rather than parents (Jessor and Jessor, 1978; Kandel et al., 1978a; Brook et al., 1980). Contact with other users increases the likelihood that the individual will have increased opportunities to get the drug. Peer-mediated approaches have been shown to be an effective vehicle for interventions to prevent smoking of tobacco in adolescents (Evans, 1977; McAlister, 1979). The powerful role of peer influence on the use of marijuana would seem to suggest that it would be also useful for preventive marijuana programs.

SUMMARY

There has been a steep rise in the use of marijuana and other illicit drugs in the past decade. So far it is primarily a youth phenomenon. Since 1971 there has been at least a doubling of lifetime experience with marijuana in every cohort in the 12- to 24-year age group. Of all psychoactive drugs investigated (including inhalants, hallucinogens, cocaine, heroin, stimulants, sedatives, and tranquilizers), marijuana is by far the most commonly used illicit drug. Legal drugs for adults, such as alcohol and tobacco, are the most widely used of

all drugs among adolescents. Although substantially more students have ever used alcohol in their lifetime than have ever used marijuana, more high school seniors use marijuana on a "daily" basis (9 percent) than use alcohol that frequently (6 percent). "Daily" users report the use of marijuana in school, whereas daily use of alcohol tends to occur after school and on weekends.

Some trends in use of marijuana are apparent. The continuing dramatic rise in the use of marijuana has recently slowed. It is too early to tell whether this decrease will continue or is merely a pause in the rise. The overall prevalence of use of marijuana has remained at approximately 60 percent of high school seniors for the years 1978, 1979, and 1980. Between 1975 and 1978 there was an almost twofold increase in "daily" use of marijuana from 6 percent in 1975 to a peak rate of 11 percent in 1978. In 1980 the "daily" use rate of high school seniors dropped by 1.2 percentage points, or more than 10 percent. This may signal a reversal of the upward trend in "daily" use unless higher absenteeism and school drop-out of daily users are significant factors in the decline. Multiple sources suggest that out-of-school age mates are heavier users than those in school. Other trends have not slowed. There was a continuing rise in 1980 of the proportion of high school seniors who during the year had used some illicit drug other than marijuana, from 28 percent in 1979 to 30 percent in 1980.

Throughout the 1970s, as a correlate of continuing rise in prevalence rates, there was a trend toward younger ages of first use of all of these drugs. For marijuana this age trend continues but has slowed somewhat. In 1979, 23 percent of seniors who had used marijuana started their use in the eighth grade or below as compared to 25 percent in 1980.

"Daily" use of marijuana in high school and in early adult life is very high and merits special attention. Drawing on data from Monitoring the Future, characteristics of "daily" users were described. For high school seniors the rate of "daily" marijuana use in 1980 was 9.1 percent. Such users have very high involvement with other drugs and begin their use of drugs at very early ages. "Daily" users are predominantly urban although rates do not vary by geographical regions of the country, whereas use among white students is double that for blacks. "Daily" use is only slightly higher in disrupted or single parent homes than in nuclear families, and use is associated with poor school achievement, absenteeism, and dropout. Non-college-bound students are twice as likely to be "daily" users as were students planning to attend college. Religious commitment and self-ratings of strong belief in law-abiding behavior are associated with lower "daily" use rates. "Daily" users are involved in more automobile accidents and delinquency.

Post-high school "daily" user rates are lowest among full-time college students and those living in a college dormitory. "Daily" use among non-college students was not related to joblessness, employment, or military service. Single persons are twice as likely as married persons to be "daily" users. Among the married, those with children had very low rates of "daily" use. The "daily" use

habit has a remarkable stability. By 4 years after high school, 85 percent of "daily" using seniors in the class of 1975 were still using marijuana, with 51 percent of them continuing to be "daily" users.

In these studies, students report reasons for using marijuana: to have a good time with friends, to get "high," to relieve boredom, to enhance the effects of other drugs, and to cope with stress. "Daily" users are deeply immersed in a drug-using circle of friends.

Some "daily" users have discontinued their habit. Reasons given for stopping use of marijuana are loss of interest in getting "high," concern about harmful physical or psychological effects, and concern about their loss of energy or ambition.

More is known about the antecedents of using marijuana than is known about the consequences of using marijuana (to be discussed further in the chapters that follow). Longitudinal studies have established that use of marijuana is preceded by acceptance of a cluster of beliefs and values that are favorable to use of marijuana and also by the adoption of deviant behaviors. The deviant psychosocial attributes of marijuana users that were described almost a decade ago, when use of marijuana was a rare event, are just as characteristic of marijuana users today, when 60 percent of all high school seniors report some experience with the use of marijuana. Daily users show the extremes of these deviant behaviors but less deeply involved users also exhibit some deviancy. Friendship patterns and peer influence play a uniquely powerful role in determining youthful marijuana use. Negative parental relationships do not appear to be associated as an antecedent to use of marijuana.

RECOMMENDATIONS FOR RESEARCH

Additional research needed includes (1) epidemiologic studies on patterns of use of drugs among young adolescents, including those who leave school, (2) longitudinal studies to investigate the antecedents and consequences of use of marijuana, and (3) studies of the effects of marijuana in combination with use of other drugs.

Because samples of high school seniors exclude youths most at risk for high marijuana involvement, namely adolescents not regularly attending the high school, additional cohort-sequential epidemiologic surveys beginning with prepubertal children are needed in order to follow development and behavior from early in life. An all-conclusive approach would be both a prospective (concurrent) cohort study and a retrospective case-control study of possible outcomes of and risk factors for marijuana use (this recommendation is described in detail in Chapter 6).

"Daily" users have been understudied and may have the most severe risk in terms of loss of learning potential, biological risk, and psychosocial handicap. Studies should be undertaken to predict who among the large numbers of young people who try marijuana are at risk of becoming "daily" users.