Marihuana (II): Does It Damage the Brain?

The possibility that marihuana use may be hazardous has produced a remarkable polarization among scientists. Those who say that marihuana poses no special hazards espouse their convictions with an evangelistic zeal that borders on fanaticism. Those who think there are hazards argue their case with only slightly less fervor, and all too often scientific debate has fallen by the wayside. This polarization is reinforced by the mass of contradictory evidence that seems to lend support to both sides. The naive individual seeking guidance is often hard-pressed to know whom to believe.

Enough evidence has accumulated in the past 5 years, however, that a dispassionate observer must be forced to two conclusions. There is probably little or no hazard associated with the use of a single joint—or even a few joints—but there is enough evidence suggesting potential dangers from long-term, heavy use of marihuana that prudence would dictate both caution and concern. These dangers include, among other things (*Science*, 23 August, p. 683), the possibility that long-term, heavy use of marihuana may produce sharp personality changes that lead to a marked deterioration in what is normally considered good mental health and may cause potentially irreversible brain injury. If this evidence is corroborated, cannabis (the generic term for marihuana and the more potent hashish) would have to be considered far more hazardous than was previously suspected.

There is little question that cannabis has a number of short-term effects on the brain—it could not be psychoactive if it did not. These effects include alterations in the concentrations of biogenic amines, such as serotonin and norepinephrine; changes in the activity of enzymes, such as acetylcholinesterase; and variations in electrical activity as measured by an electroencephalograph. The consequences of these short-term effects are uncertain, but few scientists seem willing to suggest that these effects are in themselves hazardous. What is of greater concern is the possibility that continuation of these effects over a period of time may produce organic brain damage.

Tetrahydrocannabinol, the principal psychoactive constituent of cannabis, has a very high affinity for brain and other lipophilic tissues, that is, tissues with a high proportion of hydrocarbon-like components. According to W. D. M. Paton of the University of Oxford, tetrahydrocannabinol has an octanol : water partition coefficient of about 6000 : 1. This coefficient is of the same order of magnitude as those of the long-lived pollutants DDT and polychlorinated biphenyls, and indicates that tetrahydrocannabinol will be absorbed by lipophilic tissues and stored by them for long periods.

Julius Axelrod of the National Institute of Mental Health, Bethesda, Maryland, has shown that only barely detectable concentrations of tetrahydrocannabinol are present in the brain of a rat after one dose; most of the tetrahydrocannabinol appears in fatty tissues. With repeated administration, though, there is a gradual buildup of the drug and its metabolites in the brain. How long it persists there is still unknown, but Axelrod has found tetrahydrocannabinol and its metabolites in the urine of the rat as long as 8 days after administration of a single dose.

The Amotivational Syndrome

The effects of this persistence are a subject of debate, but many scientists argue that the continued presence of tetrahydrocannabinol in the brain induces a set of mental characteristics termed the "amotivational syndrome." This syndrome is familiar to most clinicians who have treated cannabis users, and has perhaps best been described by psychiatrists Harold Kolansky and William T. Moore of the University of Pennsylvania, Philadelphia.

Kolansky and Moore treated 13 individuals between the ages of 20 and 41 years who had smoked cannabis three to ten times a week for at least 16 months. All showed the same set of symptoms: The patients were characteristically apathetic and sluggish in mental and physical responses. There was usually a goallessness and a loss of interest in personal appearance. Considerable flattening of affect gave a false impression of calm and well-being; this was usually accompanied by the patients' conviction that they had recently developed emotional maturity and insight aided by cannabis. This pseudoequanimity was easily disrupted if the patients were questioned about their personality change, new philosophy, and drug consumption, or if their supplies of cannabis were threatened. The individuals were physically thin, often appeared tired, and exhibited slowed physical movements. They also showed symptoms of mental confusion, a slowed time sense, difficulty with recent memory, and an incapability of completing thoughts during verbal communication.

The stereotyped nature of these symptoms and the apparent psychological stability of the patients prior to cannabis use led Kolansky and Moore to hypothesize that the syndrome was attributable to cannabis. This hypothesis was supported by the strong correlation between the severity of the symptoms and the duration of cannabis use. It was further strengthened by the observation that the syndrome disappeared when the patients abstained from use of cannabis (although some other investigators have attributed this disappearance to the combination of therapy and the power of suggestion). In those patients who had used cannabis most heavily and then stopped, however, the symptoms persisted intermittently for as long as 24 months, and the investigators suggest that these individuals may have suffered irreversible brain damage.

Kolansky and Moore have observed the syndrome in another 38 younger cannabis users (from 13 to 24 years of age), and their observations are corroborated by the experience of some other clinicians, such as Hardin B. Jones of the University of California at Berkeley. Certain aspects of the syndrome have also been corroborated in controlled studies. One of these studies, moreover, apparently reverses the conclusions of an earlier study that had failed to demonstrate the syndrome.

Two years ago, Jack H. Mendelson and Roger E. Meyer of Harvard Medical School's Alcohol and Drug Abuse Research Center at McLean Hospital, Belmont, Massachusetts, reported that they observed no evidence of the amotivational syndrome in 20 experienced cannabis users who were kept in a research ward for 21 days. The subjects were allowed to earn money and cannabis cigarettes—up to certain limits—by participating in various testing procedures. Mendelson and Meyer found that there were no indications of decreased motivation to work and no discernible effects on the ability to improve performance in various tests involving practice or on performance on tests of mental or motor function.

Mendelson and Meyer will soon report, however, on further experiments

of the same type, but in which there was no limit on the amount of money and cannabis that could be earned. In these experiments, they observed that certain individuals showed a marked dose-related decrease in motivation and in performance on the tests. This phenomenon was especially apparent, they say, among the light and moderate cannabis users who quickly began to smoke very heavily.

Reese Jones of the University of California's Langley-Porter Neuropsychiatric Institute in San Francisco has observed cannabis users under similar conditions, but with higher doses of tetrahydrocannabinol—as much as 210 milligrams per day, or the equivalent of two packs of marihuana cigarettes. At these doses, he says, tetrahydrocannabinol produces a strong depression of the central nervous system similar to that effected by sedatives and tranquilizers. This effect is accompanied by a loss of motivation and an impaired performance on standard tests of mental function.

Jones also finds, however, that tolerance to these doses develops within a week and that motivation and functioning are at least partially restored. This tolerance, and some of the physiological effects that accompany withdrawal, lead him to conclude that cannabis produces physical dependence. He also concludes that heavy use of cannabis produces many of the same problems as abuse of tranquilizers, sleeping pills, and the like.

Sidney Cohen of the University of California Medical Center at Los Angeles is one of the few other investigators to conduct controlled studies with cannabis. He observes the subjects for 93 days, three times as long as the other investigators. Like Jones and others, he observes that tolerance to cannabis develops rather quickly, but he has not observed a loss of motivation or of mental function. He concedes, though, that there may be subtle mental changes that he is not able to measure.

Leo Hollister of the Veterans Administration Research Hospital in Palo Alto, California, has examined many of the effects of single doses of cannabis. He finds that cannabis, like alcohol and some other drugs, seems to disrupt the transfer of information in the brain from short-term to long-term memory. Information acquired while under the influence of cannabis would thus be forgotten more easily than if it were acquired while sober; subjects would also have difficulty completing their thoughts during conversations. Hollister also finds, however, that there are no apparent long-term effects from a single or an occasional use of cannabis.

Most of the other evidence bearing on the possibility of brain damage has been obtained under much less rigidly controlled conditions. One of the most controversial pieces of evidence has been provided by the late A. M. G. Campbell and his associates at the British Royal United Hospitals, London. They obtained air encephalograms —a type of x-ray in which air is injected into the brain cavity—of the brains of ten young males who had used cannabis very heavily for 3 to 11 years. Close comparison with air encephalograms of carefully matched controls suggested that the brains of the users had physically atrophied. Campbell attributed this atrophy to the use of cannabis, but other investigators have argued that the subjects also used vasoconstrictive drugs, such as amphetamines and LSD, that could be responsible for the observed effects. Little follow-up to these studies has been reported, in part because the process of air encephalography is itself painful and potentially hazardous.

Some Show Intermittent Symptoms

Forest S. Tennant, Jr., and D. J. Groesbeck of the University of California Medical Center have reported on studies of some 110 U.S. Army soldiers who used hashish very heavily and exhibited symptoms similar to those observed by Kolansky and Moore. They were able to monitor nine of these patients who voluntarily abstained from use of hashish. Six of the nine apparently returned to normal within 2 to 4 weeks after quitting, but three continued to exhibit intermittent symptoms of brain dysfunction during the entire 2 years in which they were observed. Another 10 of the 110 also had such recurring symptoms after claiming to have quit using hashish, but the investigators had no objective confirmation of their abstention.

M. I. Soueif of Cairo University examined 850 Egyptian hashish users imprisoned for various crimes and compared their mental and motor functions to 839 matched controls, also prisoners. He found that, on the average, the hashish users performed more poorly than the controls on all tests. In particular, Soueif claims that the magnitude of intellectual impairment appeared to be directly related to the general level of proficiency prior to the use of hashish: the higher the initial proficiency, the greater the apparent impairment. Soueif's results have been criticized, however, on the grounds that they may simply reflect a long-term existence is a particular life-style necessitated by participation in the hashish subculture of Egypt.

One set of animal experiments is also of interest in considering the possibility of brain damage. Many investigators, employing electrodes attached to the scalps of primates, have found a variety of inconsistent changes in electroencephalograms obtained during the subject's use of cannabis. But Robert G. Heath of Tulane University, New Orleans, has performed such experiments using electrodes embedded at specific sites deep within the brain. These sites had previously been found by Heath to be associated with emotional responsivity, alerting, and sensory perception.

When rhesus monkeys with the implanted electrodes were exposed to cannabis or tetrahydrocannabinol, Heath observed consistent and distinct changes in the electroencephalograms. And when the monkeys were exposed to the agents at moderate or high doses over a period of time, persistent—perhaps irreversible—alterations of brain function appeared at those sites. This result has been interpreted by some investigators as a narcotization of pleasure centers in the brain. Postmortem examinations of some of the animals suggested that structural alteration of brain cells may be associated with the persistent physiological changes.

In summary, then, it seems likely that the putative link between heavy long-term use of cannabis and possible brain damage will remain controversial for some time to come. This is true, in part, because there are few accurate, easy to perform, and relatively specific tests available for detecting brain damage, particularly if it is subtle. Moreover, it also seems likely that the adverse effects of cannabis are manifested in only a fraction of susceptible cannabis users, so that larger sample populations will be necessary to observe them. But whatever the case, there seems to be enough evidence suggesting the possibility of brain damage that discretion would require avoiding the risk.

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