Marihuana: The Grass May No Longer Be Greener

The notion that marihuana is harmless has enjoyed a high degree of acceptability with only a minimum of scientific support. Several respected publications and many respectable individuals have advocated legalization of marihuana on the basis of what amounts to little more than an assumption that it is harmless. At least some of these individuals, however, seem to have ignored the growing body of evidence that indicates otherwise. Since 1969, when the federal government began making marihuana of controlled quality available to research scientists, evidence suggesting potential hazards has accumulated at a rapid pace. Those 5 years of research have provided strong evidence that, if corroborated, would suggest that marihuana in its various forms may be far more hazardous than was originally suspected.

That is not to say that one joint of marihuana—or even a few joints—will cause significant harm: the chances are it will not. What the evidence does suggest is that the effects of marihuana are cumulative and dose-related, and that prolonged heavy use of marihuana, or less frequent use of the more potent hashish, is associated with at least six different types of potential hazard. The research indicates that cannabis (the generic term for both hashish and marihuana):

► May cause chromosome damage that could affect the health of the user.

► May cause disruption of cellular metabolism, including synthesis of DNA, and may interfere with the functioning of the immune system.

► May mimic hormones or act on hormonal regulators to produce a variety of effects ranging from impotence and temporary sterility to the development of female-like breasts in men.

► Is, with heavy use, severely debilitating to the bronchial tract and lungs.

► Causes sharp personality changes that lead to a marked deterioration in what is normally considered good mental health.

► And, most important, may cause potentially irreversible brain damage.

A great deal of controversy has surrounded the fact that the evidence for some of these potential hazards is derived from the clinical experience of physicians and psychiatrists with relatively few self-confessed cannabis users. Most investigators recognize that this type of evidence has inherent limitations. The subjects have generally used illicitly obtained cannabis whose potency (and identity) is difficult to assess; many of the subjects have also used other licit or illicit drugs; and a reconstruction of the subject's history of cannabis use relies entirely on the subject's potentially faulty memory.

Clinical observations are thus less reliable than evidence obtained in controlled trials where all aspects of the subject's drug use can be monitored. Nonetheless, clinical observations may provide the only evidence available about long-term use of cannabis. If any of the current evidence suggesting multiple hazards from long-term exposure is corroborated, most investigators would consider it ethically indefensible to subject a volunteer to such exposure in clinical trials. It thus seems quite likely that the evidence of hazard associated with prolonged exposure to cannabis will be the subject of continuing controversy.

Possible Chromosome Damage

One potential hazard that has been the subject of such controversy is the possibility that exposure to cannabis causes damage to chromosomes. The primary evidence suggesting such a hazard has been developed by Morton A. Stenchever and his associates at the University of Utah School of Medicine, Salt Lake City. Stenchever examined leukocytes from 49 individuals who had used cannabis for an average of 3 years and found an average of 3.4 leukocytes with chromosome breaks per 100 cells per subject. This figure was more than twice as high as the average of 1.2 cells with breaks per 100 cells that he observed in 20 matched individuals who did not use cannabis, but is of the same magnitude as that associated with many ethical drugs. The observed incidence of breakage is, according to Hardin B. Jones of the University of California at Berkeley, comparable to the damage associated with high doses of ionizing radiation (150 roentgens) and has the same potential for hazard.

Stenchever found no statistically significant difference between the breakage rate in the 27 individuals who used cannabis two or more times per week and the rate in the 22 who used it less often. Nor was there a difference in the rates of the 22 who used other drugs and the 27 who did not. These categories were not mutually exclusive, however, and thus the distinctions may be ambiguous.

Stenchever's results differ slightly from earlier findings of Douglas G. Gilmour and his associates at New York University School of Medicine, New York City. Gilmour found comparable increases in the incidence of chromosome damage in 11 individuals who used cannabis more than twice a month, but found no increase in the incidence among 30 individuals who used it less often. Most of the individuals showing increased breakage were also using other drugs. Somewhat different results were also obtained by Akira Morishima of the Columbia University College of Physicians and Surgeons in New York City. He examined leukocytes from three individuals who had used cannabis at least once a week for a year or more and found that 30 percent of the cells contained only 5 to 30 chromosomes, compared to the normal human complement of 46. Morishima found similar abnormal numbers of chromosomes in only 7 percent of leukocytes from healthy individuals.

Other studies have produced seemingly contradictory results. Warren W. Nichols of the Institute for Medical Research, Camden, New Jersey, examined leukocytes from 24 individuals (with limited prior exposure to cannabis) who had been given cannabis under controlled conditions for as long as 12 days. He found no evidence of an increased incidence of abnormalities. Henry B. Pace and his associates at the University of Mississippi, University, found no increase in abnormalities in cultured rat cells exposed to cannabis smoke.

Richard L. Neu of the Upstate Medical Center, Syracuse, New York, and, independently, Stenchever found no increase in abnormalities in cultured human leukocytes exposed to tetrahydrocannabinol, the principal psychoactive ingredient in cannabis. But Cecile and Rudolph Leuchtenberger of the Swiss Institute for Experimental Cancer Research, Lausanne, have observed

a high incidence of both damaged chromosomes and abnormal numbers of chromosomes in cultured mouse and human lung cells exposed to cannabis smoke. Some of these contradictions, Stenchever suggests, undoubtedly result from differences in methodology. Other contradictions may reflect the possibility that the observed damage is caused by some ingredient in cannabis smoke other than tetrahydrocannabinol.

If the observations of chromosome abnormalities are corroborated, it seems likely that they may prove to be gross manifestations of more subtle developmental lesions. Chromosome counts and observations are generally made while the cells are in metaphase, the stage of mitosis in which the DNA has been copied and gathered into chromosomes, but the cell has not begun to split in two. Interference with the process of DNA synthesis, for instance, could thus produce chromosome abnormalities.

Convincing evidence in support of this possibility has been offered by Gabriel G. Nahas of the Columbia University College of Physicians and Surgeons. He and Morishima obtained lymphocytes from 51 individuals who had used cannabis an average of four times per week for an average of 4 years and subjected the lymphocytes to standard laboratory tests that measure their capacity to respond to mitotic stimulants, such as phytohemagglutin. They found that the incorporation of nucleic acids—and thus DNA synthesis—was about 40 percent lower in the lymphocytes from cannabis users than it was in comparable cells from nonusers. Nahas has obtained similar results in rodents and, with Carolyn Daul of Tulane University, New Orleans, in rhesus monkeys. He has also observed a depression of DNA synthesis in lymphocytes exposed to cannabis extracts in vitro. These experiments with cultured cells show that the nonpsychoactive components of cannabis, cannabinol and cannabidiol, are more effective than tetrahydrocannabinol in depressing DNA synthesis, lending support to Stenchever's contention that a nonpsychoactive component is responsible for chromosome aberrations.

Because lymphocytes are involved in the phenomenon known as cell-mediated immunity, Nahas argues that long-term use of cannabis lowers the immune responsiveness of a user and thus makes him more susceptible to disease. He notes in support of this hypothesis that the magnitude of the depression of DNA synthesis in cannabis users is similar to that observed in cancer patients (who are believed to suffer immune impairment) and in transplant patients who have been subjected to long-term immunosuppressive therapy. Although few scientists appear willing yet to acept Nahas's conclusions about impairment of the immune system, there is support for his observations of depressed DNA synthesis.

Louis S. Harris and his colleagues at the Medical College of Virginia, Richmond, have extended Nahas's observations by showing that tetrahydrocannabinol depresses immune responsiveness in mice. In one set of experiments, Harris showed that orally administered tetrahydrocannabinol will delay the rejection of black (BDF) skin grafted onto incompatible white (Nylar-A) mice by as much as 42 percent. This prolongation of graft survival is comparable to that achieved with the classical immunosuppressive drugs and suggests that tetrahydrocannabinol is interfering with cell-mediated immunity.

An Antitumor Agent

In another series of experiments, Harris showed that orally administered tetrahydrocannabinol (bound to bovine serum albumin) has little if any effect on DNA synthesis in brain, testis, spleen, or bone marrow tissue in mice, but depresses DNA synthesis by as much as 75 percent in two types of transplanted malignant tumors (Lewis lung carcinoma and mouse mammary carcinoma). The tetrahydrocannabinol increased the life-span of the mice with tumors by as much as 36 percent, which compares favorably with the 45 percent extension of survival produced by the antitumor agent cyclophosphamide. While these results indicate that there may be some valid medical uses for cannabis, they also suggest that—as with any potent drug—there may be hazards with casual use.

In contrast to Harris's results, however, Phyllis J. Lessin and Melvin J. Silverstein of the University of California at Los Angeles have been unable to observe any effects of cannabis on immunity. They performed standard skin patch tests with 2,4-dinitrochlorobenzene on more than 30 individuals who had smoked cannabis at least three times a week for 6 months or more and obtained a positive response in every instance. A positive response to such tests—obtained in about 96 percent of the normal population—is generally considered an indication that the subject has the capacity to mount a cell-mediated immune response. Their findings suggest, Lessin says, that even if Nahas's in vitro findings are correct, other components of the immune system may compensate for the lymphocytes.

Other investigations of the putative link between cannabis and alterations in cell metabolism have been somewhat more fragmentary. Preliminary results obtained by the Leuchtenbergers, for example, indicate that DNA synthesis is depressed in cultured human lung tissue exposed to cannabis smoke. This depressed synthesis appears to be associated with marked abnormalities in the DNA content of chromosomes. Arthur M. Zimmerman of the University of Toronto has shown that tetrahydrocannabinol reduces cell growth, delays cell division, and interferes with the metabolism of *Tetrahymena pyriformis*, a unicellular ciliated protozoa. When the organism was placed in a 9.6-micromolar concentration of tetrahydrocannabinol, for example, Zimmerman found that RNA synthesis was depressed 70 percent, DNA synthesis was depressed 30 percent, and protein synthesis was depressed 35 percent.

Harris Rosenkrantz and his associates at the Mason Research Institute, Worcester, Massachusetts, have shown that high doses of tetrahydrocannabinol (the equivalent of as much as 50 times the amount in one human dose of hashish) administered to rats daily for 28 days produce a marked dose-related loss of acetylcholine esterase activity, protein, and RNA in the brain. But subsequent investigations by Rosenkrantz with doses more closely related to those consumed by humans do not show these effects. Rather, they show only a significantly increased oxidation of glucose by the brain and a marked increase in the production of adenosine triphosphate. The significance of these observations is not yet clear.

Another aspect of metabolism that appears to be disrupted by cannabis is hormonal activity. By interfering with organs that regulate hormones or by substituting for certain hormones, some investigators suggest, cannabis is able to produce several undesirable effects. The most conspicuous of these is an interference with the fertility of males.

Robert C. Kolodny and his associates at the Reproductive Biology Research Foundation, St. Louis, have studied 20 young men who had used cannabis at least four times a week for 6 months or longer. They found that the concentration in the blood of the male hormone testosterone was an average 44

percent lower in these men than in comparable controls; the concentration was lowest in those men who used cannabis most frequently. Six of the men had diminished sperm counts, some to the point indicating sterility, and two had impaired sexual function. Two other foundation patients not in the study were observed to have a similar impairment that was also apparently associated with cannabis use. Three of the four voluntarily refrained from using cannabis, and their sexual functioning was restored.

Several of Kolodny's subjects were given standard tests to measure their capacity to produce testosterone and all responded normally. This suggests, Kolodny says, that the effect of cannabis is not directly on the male sex organs but rather on a regulatory center such as the pituitary gland or the hypothalamus. This possibility is supported by Kolodny's observations with four male subjects who smoked one cannabis cigarette after abstaining for at least 2 weeks. He found that the concentrations of testosterone dropped by as much as 36 percent within 3 hours after smoking cannabis.

That cannabis can interfere with these regulatory organs is also suggested by experiments of Harold F. Hardman of the Medical College of Wisconsin, Milwaukee. Hardman and others have observed that cannabis interferes with the body's ability to regulate temperature. If mice, for example, are placed in an enclosure at 10° to 20°C and given tetrahydrocannabinol, their body temperatures will fall from the normal level of about 40°C to the ambient temperature. Several lines of evidence developed by Hardman indicate that this phenomenon is mediated by a central regulator of heat production, presumably the hypothalamus. This observation, like those of Harris, has potential medical utility, but it also illustrates the great variety of potentially harmful effects of cannabis.

Kolodny's observations have received mixed support. Jack H. Mendelson and Roger E. Meyer of Harvard Medical School's Alcohol and Drug Abuse Research Center at McLean Hospital, Belmont, Massachusetts, will soon report that they found no depression of testosterone concentrations in the blood of heavy users of cannabis under controlled conditions. Mendelson suggests that Kolodny's observations may result from the use of other drugs by the patients. In contrast, the Leuchtenbergers observed a marked disturbance of spermatogenesis in mice that inhaled the smoke from a total of about 100 cannabis cigarettes during a period of 3 months. Not only was there a reduced number of mature sperm in these mice, but also many of the sperm carried a less than normal amount of DNA.

Other evidence is derived from clinical observations. John A. S. Hall of the Kingston Public Hospital, Kingston, Jamaica, has examined a large number of individuals who smoke, or drink tea made from, ganja, a cannabis variant widely used in Jamaica. He says that among males who have smoked ganja for at least 5 years, the incidence of impotence is 20 percent. A perhaps somewhat lower incidence of impotence and failure to impregnate has also been observed among long-term cannabis users by Harold Kolansky of the University of Pennsylvania School of Medicine, Philadelphia, and others.

Another putative hormonal effect of cannabis that has been less well documented is the production of female-like breasts in young men. This phenomenon, known as gynecomastia, can result from many causes. Menelaos A. Aliapoulios and John W. Harmon of the Harvard Medical School and Cambridge Hospital, Cambridge, Massachusetts, have examined 14 young men with gynecomastia in whom all normal causes were eventually discounted. The only factor common to these men was the long-term, heavy use of cannabis. The two investigators suggest that the structural similarity between tetrahydrocannabinol and the female hormone estradiol may be responsible for the effect. This possibility is supported by the observation that the breasts of three of the subjects shrank when these subjects voluntarily abstained from cannabis use. Aliapoulios and Harmon have also shown that the breasts of male mice can be enlarged by injections of tetrahydrocannabinol and that this effect can be blocked by drugs that block estradiol action. Their observations have not yet been corroborated by other investigators, however.

One type of potential hazard from exposure to cannabis that is not controversial is its deleterious effect on the throat and lungs. Nearly every physician who has treated users is familiar with the sore throats and bronchial irritation that arise from the use of cannabis. Forest S. Tennant, Jr., of the University of California Medical Center at Los Angeles, for example, has reported a survey conducted among 492 U.S. Army soldiers who had been exposed to cannabis in West Germany. Nearly 25 percent of the soldiers reported that they had suffered sore throats from smoking cannabis, and some 6 percent reported that they had suffered from bronchitis. Tennant's findings are consistent with the clinical experience of many other physicians.

A more controversial question is whether persistent exposure to cannabis produces more severe bronchial and pulmonary effects, including lung cancer. Marihuana cigarettes contain about 50 percent more "tar"—the presumed carcinogenic component of tobacco—than do commercial high-tar cigarettes, and this marihuana tar induces tumors when painted on the skin of mice. There is some evidence to suggest that it has the same effect in lungs.

Tennant, Roderick Guerry, now at the University of South Carolina at Columbia, and Robert Henderson of the U.S. Army Hospital in Wurzburg, West Germany, performed bronchial biopsies on 30 young soldiers (average age: 21 years) who had smoked more than 25 grams of hashish per month and who had been diagnosed as having chronic bronchitis. Twenty-four of the 30 had abnormal bronchial biopsies similar to those of individuals who have smoked tobacco for many years; the biopsy results revealed many lesions characteristic of the early stages of cancer. Preliminary observations by the Leuchtenbergers indicate that similar lesions are observed in the lungs of mice that have been subjected to prolonged inhalation of cannabis smoke. Both studies suggest that the tumorigenic effects of cannabis are manifested much more rapidly than those of tobacco.

W. D. M. Paton of the University of Oxford in England says that there is an increasing incidence of emphysema among young members of the drug culture. Since emphysema is normally a disease of later life, he suggests that smoking cannabis may be the cause of the increase. This possibility is buttressed by the observations of John Hall, who says that an emphysema-bronchitis syndrome is common among young Jamaican laborers who habitually smoke ganja.

In contrast to the relative unanimity of opinion about the deleterious effects of cannabis on the lungs, there is a great deal of controversy about its effects on the brain and the central nervous system. That controversy will be the subject of a second story to appear next week.—THOMAS H. MAUGH II