

The Toxicity of *Cannabis sativa* (Marihuana)



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"**C**ANNABIS CONSISTS of the dried flowering tops of the pistillate plants of *Cannabis sativa* Linne (Fam. Moraceae)" in U.S.P. XI. *Bhang* contains selected dried larger leaves and young twigs. *Ganga* consists of the tops of cultivated female plants, obtained directly after flowering. *Hashish* (*charas*) consists of compact masses of resin squeezed from the hemp leaves. These words have been used more or less interchangeably under the title "marihuana."

My investigations with marihuana started under the auspices of the Federal Bureau of Narcotics with the late Dr. Lyster Dewey, on plants then under cultivation in the fields where the Pentagon is now located. The studies were supplemented by tests on material grown in Pennsylvania. Chemical studies have suggested that some of the

isomeric tetrahydrocannabinols are related to its physiologic activity. This is of importance because of the great differences in content in the active resin when grown under different climatic and soil conditions in various parts of the world. Confirming the literature, material grown in Asia is richer in active resin than that grown in the United States. Improper drying methods will cause further decreases in active constituents. As some portions of the resin are attached to stems and seed, some degree of activity has been demonstrated for them. Also, removal of the male plants from the fields under cultivation tends to produce a higher yield of more potent resin in the residual female plants.

A thousand years ago the product hashish was reported to be used by certain Asian rulers for the stimulation of the fighting ability of their troupes... leading to the term "assassin." During the 19th century, extracts of the dried leaves of the female plants, as tinctures, fluid extracts, or solid extracts, were suggested for medical use as delirants, anodynes, aphrodisiacs, anesthetics, antiseptics, as well as for the "cure" of acne, infertility, rabies, strychnine poisoning, and cancer. Pharmacologic studies finally led to discontinuance of all such uses, except addition of the tincture to various

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corn cures because of the green color from the chlorophyll therein. U.S.P. XI recommended bioassay by comparing canine ataxia in sensitive dogs with that produced by a reference standard sample on the same animals. Such bioassays confirmed human trials in showing great variations in potency, as well as losses in activity during storage. Because of the lack of reputable clinical indications, Cannabis has been discontinued from legitimate medical practice. In the testimony before the Congress in connection with the passage of the Marihuana Tax Act of 1937, it was developed that there was no medicinal use for Cannabis or any of its preparations.

Early volunteers (particularly among the criminal classes) conducted experiments with marihuana, based on the alleged euphoric effects, and such adventures appear to become more prevalent as time passes. The pharmacologic effects produced by marihuana, especially when smoked, have been reported frequently. The principal action appears to be production of hallucinations; distortions in color, lengthening of time, and shortening of space evaluations. There is an unsolved psychiatric question whether such use produces adverse effects or releases established inhibitions. The intensity of central nervous system response varies tremendously, partly because of the different psychologic makeup of the user and the anticipated response, and partly because of the enormous variation in potency. This will be reflected in the duration of use of marihuana to produce dependence and pathologic changes.

When the Congress requested the Federal Bureau of Narcotics to assist in drafting legislation for the control of the illicit use of

marihuana, it was deemed advisable to include this in a separate act rather than to amend the Harrison Narcotic Act of 1914, which specifically pertained to control over opium and coca leaf and materials extracted therefrom. This was done by passing the Marihuana Tax Act of 1937. Some confusion developed throughout the world in connection with the recognition of the growing menace of marihuana because of the difficulties in the nature of response following its use. The Expert Committee on Addiction-producing Drugs of the World Health Organization struggled with the question of semantics for several years to clarify the proper use of the terms "addiction" and "habituation" and finally decided in 1964 to discontinue both terms in discussing drug abuse, supplanting them with the general term "drug dependence"; this general term is to be modified with respect to the particular drug to be used. They recognized drug dependence of the morphine type, of the barbiturate type, and of the marihuana type. In a further action in January 1968, the Commission on Narcotic Drugs of World Health Organization recommended that the Single Convention on Narcotic Drugs of 1961, adopted by the United States in 1968, recommends that all countries throughout the world increase efforts to eradicate abuse and illicit traffic in Cannabis, recognizing that its use may result in unpredictable behavior, violence, and adverse effects on health, and lead to the abuse of other drugs such as LSD, stimulants, and heroin. As an international treaty, these requirements would prevent possible weakening of the controls over marihuana in the United States.

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relationship between marihuana and crime. Confirming many reports from abroad, search of the records in the Bureau has shown that almost 100 individuals committed crimes of assault and battery, burglary, murder, reckless driving, and rape while under the immediate influence of smoke from marihuana cigarets.

The death of mice, rats, guinea pigs, rabbits, cats, and dogs after various methods of administration of various types of marihuana preparations has been determined. Since no reference standard material was used in these toxicity studies, as they were conducted prior to the preparation of an International Reference Cannabis Standard in 1967, it is difficult to evaluate the relative toxicities. The acute fatal dose ranges from 10 mg./kg. for rats to 250 mg./kg. for guinea pigs after oral administration; after intraperitoneal administration, from 75 to 1,000 mg./kg. depending on the interval between administration and death. In general, general paralysis of the respiration associated with both tonic and clonic convulsions developed, and death was due to cardiac failure.

Detailed studies of the literature showed development of catalepsy and hallucinations in a number of human subjects following smoking $\frac{3}{4}$ cigaret or 1-4 Gm. of dried leaves. Following oral administration, catalepsy, hallucinations, and permanent insanity developed from 15 mg. of hashish to 60 mg. of charas; 30 mg. to 12.6 Gm. of solid extract; 0.3 to 6 ml. of tincture; 50 to 100 mg. of the oleoresin. Of 200 individuals consuming bread with which Cannabis had been mixed by accident, 15 developed permanent insanity, and 4 died. In another re-

port, 6 of 95 subjects died after consuming a large quantity of *Cannabis indica*. A soldier died after oral ingestion of an unknown quantity of bhang. Chopra's made comparative tests on a series of extracts from *Cannabis indica*. Death followed charas at 2 Gm./kg.; ganga at 8 Gm./kg.; and bhang at 10 Gm./kg. The serious results following exposure to marihuana, especially when smoked, however, appear to be due to progressive, irreversible damage to various parts of the brain.

Various investigators have studied the effects of marihuana under controlled conditions throughout the world. It is the chief drug of dependence in Egypt and parts of Asia. It has been reported to produce all of the hallucinogenic effects of LSD. It renders the addict a burden to society. "Its continued use leads straight to the lunatic asylum." Investigations among heroin addicts in various parts of the world have indicated that some 90% started their downward path by using marihuana, frequently under the delusion that it was not addicting.

Summarizing, the physiologic potency of various lots of *Cannabis sativa* and preparations made therefrom show marked variations in potency. Deaths in animals are associated with catalepsy and cardiac failure. Progressive, irreversible brain damage has been observed. Humans smoking marihuana cigarets, or ingesting leaves of Cannabis or extracts therefrom, have developed hallucinations, delirium, progressive brain damage, and death from cardiac failure. "While under the influence," authentic records demonstrate the commission of various crimes ranging from assault and battery to rape and murder.

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