PHARMACOLOGICAL REVIEWS
Vol. 23, No. 4

Printed in U.S.A.

Session II

CLINICAL PHARMACOLOGY OF MARIHUANA

HARRIS ISBELL

Professor of Medicine and Pharmacology, University of Kentucky Medical Center, Lexington, Kentucky

The use of marihuana is and has been one of the most divisive social issues of our time. On the one hand, the opponents of marihuana have claimed that it causes serious antisocial behavior including murder and rape, produces insanity and is a sure ticket to non-medical use of other drugs. On the other hand, its proponents argue that marihuana is harmless, causes only happiness, and is less damaging than the legally and socially acceptable drug, alcohol. Persons on both sides of the argument are prone to use any part of any material to support their social and legal arguments and frequently do so out of context. Therefore clinical pharmacology has a tremendous responsibility for elucidating the effects of marihuana and its surrogates in man and the mechanisms of action of these drugs and for pointing out what these effects and mechanisms are in very clear terms.

Although *cannabis* is one of the oldest intoxicants in use, less is known about its pharmacology than about any other major drug used non-medically. The chief reason for our ignorance has been the difficult chemistry of *cannabis*. The exact chemical configurations of the most active materials in cannabis, the *l*-Δ^8- and *l*-Δ^9-tetrahydrocannabinols were not elucidated until 1963 and synthesis of these materials was not accomplished until 1967. The availability of the compounds through the National Institute of Mental Health and the development of chemical methods for the assay of the concentration of active cannabinoids in crude material has remedied these problems. Accordingly it can be expected that in the next few years more knowledge will be gained about the clinical pharmacology of cannabis than in all the previous 4000 years of its history. The present symposium is only a beginning.

The papers in the symposium show, as should be no surprise to pharmacologists, that *cannabis* contains a powerful psychoactive material. The *l*-Δ^9-tetrahydrocannabinol (also called Δ^1-THC) reproduces most, if not all of the effects of the crude plant drug. *The degree of change is proportional to dose when the drugs are given either orally or by smoking.* The elementary concept of the dose-response relationship is stressed here because it has been neglected in practically all the voluminous psychological and sociological literature and confusion has resulted. Many of the differences observed after smoking various forms of *cannabis* around the world may reflect chiefly the enormous variation in the concentration of the *l*-Δ^9-THC in different materials in different locales.

The most consistent objective changes in man after marihuana and its surrogates are tachycardia, conjunctival infection and increased body sway.

The subjective mental effects include elation, euphoria, sensory perceptual distortion, depersonalization, and, with high doses, hallucinations. Sedative effects

are prominent after the initial euphoriant phase. Psychologically, the most striking phenomenon appears to be impairment of ability to think in a connected fashion to a goal (impairment of recent memory?). All these phenomena vary with dose. The effects of the synthetic surrogates, $\Delta^{10a,6a}$ 5-n-hexyl-tetrahydrocannabinol (pyrahexyl) and $\Delta^{10a,6a}$ 5-n-amyl-tetrahydrocannabinol ("Adams synthetic THC") are similar to those of the *l*-Δ^9-THC although pyrahexyl and synthetic THC are less potent. The effects of crude marihuana are proportional to the content of *l*Δ^9-THC. The expectations of the subjects may greatly influence their interpretation of the effects of marihuana or placebo.

No serious toxic effects have been observed in these experiments.

The metabolism of *l*-Δ^9-THC in man is similar to that observed in animals with the 1-hydroxy derivative being formed as the first step *l*-Δ^9-THC has a shorter half-life in heavy chronic users as compared with occasional users.

Much remains to be done. Although the acute effects of a single dose in man have been reasonably well delineated, information is needed about the effects of several cigarettes consumed over a longer time period. Because of the demonstration of tolerance in animals, reinvestigation of this phenomenon in man as well as reinvestigation of the possibility of physical dependence must be done when and if sufficient information on chronic toxicity in animals becomes available. Because users generally take drugs other than marihuana information on possible interactions with opiates, amphetamines, hypnotics and hallucinogens is needed. It has already been shown that the same effects of marihuana and alcohol are addictive. Studies on the actions of other cannabinoids, such as cannabinol or cannabidiol, are needed as are investigations of possible interactions of these materials with the *l*-Δ^9-THC. Answers to these and other problems will soon be forthcoming.

The most difficult question is that of possible chronic toxic effects after months or years of continuous heavy use. This question can be investigated only by carefully controlled observations on heavy users in cultures where chronic use is common. Such investigations are already underway and will complement chronic toxicity studies in animals.