

MARIHUANA

CHEMISTRY, BIOCHEMISTRY, AND
CELLULAR EFFECTS

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Preface:

Why Another Monograph on Marihuana?

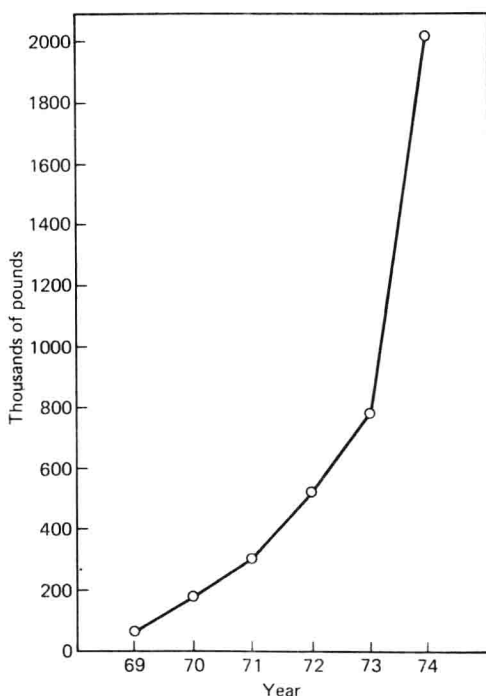
Hasn't this subject been exhausted over the past 6 years by the publication of the dozen volumes that preceded the present one? After numerous investigations on the acute effects of marihuana smoking in man described in hundreds of papers, what is left to know? Following the studies of chronic users performed in Boston, Los Angeles, Jamaica, and Greece, hasn't the marihuana question been settled?

Shouldn't we now consider marihuana a "soft drug" to be used for recreational purposes, like alcohol or tobacco, with minimal danger to the user and little damage to society? A number of scientists have already given an affirmative answer to these questions, and their opinions, amplified by the media, seem to be shared by a large section of the lay public. On the other hand, some investigators claim that old empirical observations confirmed by recent scientific evidence indicate that marihuana is a harmful drug. As a result, a great marihuana debate is now raging in the scientific and lay press of the United States. Let us hope that it will not linger as long as the tobacco debate, which was settled only a decade ago.

Meanwhile, the use of marihuana, especially by adolescents, has been spreading exponentially in countries where it was nearly unknown 20 years ago (see figure on the following page). It even seems possible that some countries are prepared to give a new legal status to this drug, thereby eliminating the social stigma attached to its use. Marihuana would no longer be considered a "stupefying drug," like opium or coca leaf derivatives, the Single Convention Treaty on Stupefying Drugs would be bypassed, and marihuana products would be made commercially available.

It is against this background that the Helsinki Symposium on Marihuana, which is recorded in this monograph, was organized under the aegis of the Sixth International Congress of Pharmacology. This symposium was called to discuss the biochemical and cellular effects of marihuana products in the general perspective of their long-term use.

Following the work of Agurell, Paton, Lemberger, and Axelrod, investigators established that the fat-soluble cannabinoids remain in tissues for days and weeks. However, routine pharmacological studies



Removals of marihuana by USA federal authorities (domestic and foreign cooperative). (In order to roughly estimate the amounts consumed, the amounts removed are usually multiplied by six.)

From "Hearings of the U.S. Senate Committee on the Judiciary (Subcommittee on Internal Security): Marihuana-Hashish Epidemic, Part II, The Continuing Escalation, May 8, 1975," U.S. Government Printing Office, Washington, D.C., 1975.

then indicated that accumulation of these foreign molecules did not seem to affect permanently any of the vital functions over weeks and months as "tolerance" to their use developed.

At the same time, studies by several cell biologists were published in close succession: Zimmerman, the Leuchtenbergers, Jakubovic, McGeer, Succiu-Foca, Armand, Nahas, and Morishima all had independently investigated the effects of marihuana products on cellular anabolism and cell division. A common conclusion emerged from their studies, which employed widely different models: cannabinoids in concentrations of 10^{-6} to 10^{-4} M inhibit the synthesis of DNA, RNA, and proteins in replicating eukaryote cells. Mechoulam's Δ^9 -THC and all natural cannabinoids tested—whether psychoactive or

not—as well as their metabolites which accumulated in tissues, inhibited cell anabolism.

These *in vitro* observations were confirmed *in vivo* by Rosenkranz: Rodents given marihuana by ingestion or by inhalation exhibited impairment of growth, spermatogenesis, and the immunity system.

A number of investigators reported the inhibitory effect of marihuana in man on pulmonary macrophages, lymphocyte function, and sperm production.

Although these results await additional confirmation, all of the present experimental evidence tends to corroborate the early *in vitro* observations which reported an impairment of cellular anabolism by cannabinoids.

Only longitudinal epidemiological studies of marihuana-smoking populations may document the pathologic effects of long-term cannabis usage. To my knowledge the literature does not contain a single autopsy report on a long-term chronic marihuana smoker. Therefore the human pathology of marihuana cannot be written before two or three decades. (It took sixty years for investigators to establish the pathology of tobacco smoking.) Meanwhile, on the basis of their present short-term observations and past experience with other drugs, biologists and physicians can only make certain predictions about what this pathology might be.

The papers contained in this monograph, inasmuch as they describe some of the interactions between the biologically active molecules contained in marihuana and the basic components and processes of living cells, might help the biologist and the physician assess the long-term effects of marihuana use on reproduction, embryological development, learning, and growth, as well as on the integrity of physiological functions.

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Helsinki, July 1975

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