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Editorial Views

The Other Side of Marihuana Research

". . . the leaves of the plant made a good snuff for deterging the brain; the juice of the leaves applied to the head as a wash to remove dandruff and vermin; drops of the juice thrown into the ear allay pain and destroy worms and insects. It checks diarrhea, is useful in gonorrhea, restrains seminal secretions, and is diuretic. The bark has a similar effect. The powder is recommended as an external application to fresh wounds and sores and for canning granulations; a poultice of the boiled roots and leaves for inflammations and erysipelas and for allaying neuralgic pains . . ."

—from *Makhsanul Aldawaiya* (a well-known Arabic book on materia medica)

TESTIMONY to the stimulant and sedative properties of cannabis and its use in medicine in other parts of the world is abundant in world literature. The Indian Hemp Commission Report of 1893 cities *Cannabis indica* as one of the most important drugs of Indian Materia Medica. In Europe nd America extracts of marihuana were used for patients with a variety of somatic and psychiatric illnesses, including migraine, depression, rheumatism, and epilepsy. Tincture of cannabis was listed in the U. S. Pharmacopeia and the National Formulary, and could be prescribed by physicians for these and other ailments. By 1940, totally synthetic isomers and homologs of the active principle of the plant were also being studied and used by various clinical investigators in the United States. However, the use of cannabis as a drug appeared to decline in the late 1930's, and by 1942 it was no longer listed in the USP. Its decline was perhaps due to the resinous, intractable nature of the natural product, to its general lack of specific therapeutic activity, and to the increasing use of other drugs for the same indications.

The demise of cannabis as a drug was not accompanied by a decline in its social abuse. The Marihuana Tax Act of 1937 was passed for the purpose of controlling its use by individuals with little or no defined industrial or medical purpose. However, the pharmacologic and toxicologic properties of cannabis and its synthetic derivatives continued to preoccupy some scientific investigators.

The virtues of cannabis, which no doubt stimulated much of the current search for useful drugs from the cannabinoid field, are: 1) The unique pharmacologic profile of cannabis and the potency of its active principle and synthetic derivatives. 2) The absence of physical dependence liability at doses commonly used by man. 3) Extraordinarily low toxicity in laboratory animals, including low lethality, and little or no respiratory depression. 4) The existence of centuries of folklore suggesting pain relief, sedation, and other therapeutic effects.

With current availability of pure synthetic cannabinoids, water-soluble crystalline derivatives,[1] highly active homologs,[2] and distantly related benzopyrans,[3] and with availability of more precise methods of pharmacologic study in animals and man, the earlier problems in identifying or discovering new therapeutic applications are being overcome.

Two papers in this issue describe the effects of Δ^9-THC, the resinous active principle of cannabis, on anesthetic requirements for halothane and cyclopropane. Treatment of animals with Δ^9-THC significantly lowered the minimum alveolar concentrations (MAC) of these anesthetics. Two sets of data, from different species with different anesthetics, provide the same significant result: a dose-related lowering of MAC. These experiments point

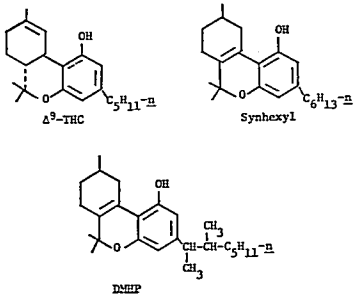

FIG. 1. Structures of Δ^9-THC, synhexyl, and DMHP.

to at least one possible area of clinical use for Δ^9-THC.

Another pharmacologic property of Δ^9-THC with therapeutic significance is its sedative hypnotic effects. In man, Δ^9-THC and synhexyl have been described as producing a "sleepy-happy high." These effects occur rapidly after oral administration in normal subjects receiving Δ^9-THC. The electroencephalogram is altered by an increment in stage IV sleep and a slight decrement in REM sleep.[4] It is well known that commonly used hypnotics produce significant decrements in REM sleep. Another difference of unknown significance is that there is no loss of righting reflex in mice with Δ^9-THC, unlike currently used hypnotics. This is unusual in view of the significant increase in barbiturate sleeping time induced by THC's, including the potent isomer-homolog DMHP [2,5] (see fig. 1).

Other reports of the pharmacologic effects of these substances suggest additional potential therapeutic areas. For example, THC's have antinociceptive action in small animals. Although variable and non-dose-related for Δ^9-THC itself, the wide range of test procedures in which THC's are active in animals indicates a good probability of efficacy in man. Other effects reported for Δ^9-THC itself include anticonvulsant action and an effect on intraocular pressure of possible value in treating glaucoma. Isolated descriptions of the treatment of the alcohol abstinence syndrome with synhexyl have appeared. Yet another synthetic analog has shown nalorphine-like precipitation of withdrawal in morphine-dependent monkeys.

A factor offsetting possible therapeutic value of Δ^9-THC and perhaps other THC's is the often neglected cardiovascular properties of these drugs. For example, although THC has no hypotensive activity in unanesthetized animals, in anesthetized animals and those with midbrain transection, a marked fall in blood pressure always follows Δ^9-THC. In addition, Δ^9-THC induces tachycardia immediately following administration to man, an effect readily prevented by β-adrenergic blockade. Of unknown significance to man is the hypothermic effect produced by Δ^9-THC in mice. In contrast to Δ^9-THC, DMPH is also potent as a hypotensive agent, produces orthostatic hypotension at doses of only a few micrograms per kilogram intravenously, and is equally active in animals. Some of the newer synthetic compounds do not have hypotensive activity in anesthetized laboratory animals. Like Δ^9-THC and DMHP, they have some analgesic effects in mice, but produce little or no respiratory depression in anesthetized dogs.[6] Differences of this type may eventually lead to new drugs, perhaps acting by different mechanisms.

Clearly, current research in this field is aimed at developing drugs with greater potency for desirable actions and with fewer of the undesirable pharmacologic properties of Δ^9-THC-like cannabinoids. It appears to this observer that the trends have finally turned to a logical sequel of the pioneering studies of the earliest recorded pharmacologist in this field, Emperor Shen Nung of China, 2737 B.C.

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