

Mechoulam R. Marijuana chemistry. *Science* 168:1159-66, 1970.  
[Laboratory of Natural Products, Pharmacy School, Hebrew University, Jerusalem, Israel]

This article critically reviewed the advances made in the isolation, structural elucidation, synthesis, chemical behavior, structural-activity relationships, and metabolism of the cannabinoids. Emphasis was placed on  $\Delta^1$ -tetrahydrocannabinol ( $\Delta^1$ -THC, or  $\Delta^9$ -THC by the nomenclature mostly used in the US), the major active component which had been isolated in pure form only a few years before. It was stressed that the area was ripe for more sophisticated biological research. [The SC<sup>i</sup> indicates that this paper has been cited in over 280 publications since 1970.]

R. Mechoulam  
Department of Natural Products  
Pharmacy School  
Hebrew University  
Jerusalem 91120  
Israel

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"In the early-1960s, I was at the Weizmann Institute in Rehovot back from a postdoctoral stay at the Rockefeller Institute in New York, and was looking for research topics of potential importance outside the heavily populated areas of current interest. I was surprised to find that the active component(s) of cannabis had never been isolated in a pure form and its structure was known only in a general way. A few cannabinoids had been reported but the structure of only one, the psychotropically inactive cannabinol, had been fully elucidated.<sup>1,3</sup>

"In 1962, I convinced the Israeli police to give me a few kilograms of confiscated hashish, and Yuval Shvo and I reisolated cannabidiol, a constituent which Roger Adams and Lord Todd had found in marijuana.<sup>4,5</sup> We elucidated its structure and stereochemistry.<sup>6</sup> A close friend and colleague, Yehiel Gaoni, became interested and we joined forces. An application for a National Insti-

tute of Mental Health (NIMH) grant was submitted, but was turned down. We were told that marijuana was not much of an American problem and that NIMH was not planning to support research in this area. The year was 1964! A year later, D. Efron, head of the pharmacology section of NIMH, flew over to see us and suggested that on second thought his institute should support our work. He told us that marijuana had now become an American problem and that even the son of a prominent US politician had been found in possession of the drug. Our research had become 'relevant.' Indeed, NIMH and later the National Institute on Drug Abuse generously supported our research for 16 years.

"In the meantime Gaoni and I continued the isolation, structural elucidation, and synthesis of natural cannabinoids.  $\Delta^1$ -THC, the major active component, was isolated in 1964,<sup>7</sup> shortly to be followed by numerous others. Soon thereafter we published a synthesis of the *dl*-form of  $\Delta^9$ -THC, and in 1967, after I had moved to Jerusalem, we found a simple synthetic route to the natural (-) form of  $\Delta^1$ -THC.<sup>8</sup> A pharmacologist, Haviv Edery, took upon himself the testing of these compounds in monkeys. Other groups, in the US, Switzerland, England, and Germany, had also started publishing in this area.

"Most of the publications on cannabinoids until then were chemical in nature. However, it was evident that in the coming years much of the significant work would be on metabolism, pharmacology, and clinical aspects. Hence I decided to summarize the chemical background obtained till then for a biologically oriented general journal. I also introduced in this concise review speculations on the existence of active metabolites. This review apparently filled a gap. It also popularized the term 'cannabinoids' which we had introduced earlier.

"This paper has been highly cited for the following reason. Numerous groups in the early-1970s working on the various biological effects of THC, which had become available in part due to our contributions, preferred to cite this review rather than the original publications. As THC became a widely used term few of the thousands of papers describing its action continued to cite the chemical background. Cannabinoid research had come of age."<sup>9,10</sup>

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