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Cannabinoids as Therapeutics

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Preface

Twenty years ago the endocannabinoid system was unknown. We knew much about the use over millennia of *Cannabis* plant preparations both as a medicine and as “a drug that takes away the mind” (as so-well stated in ancient Assyrian clay tablets). During the early part of the last century considerable progress was made on the chemistry and pharmacology of *Cannabis*, but it was only after the identification in 1964 of Δ^9 -tetrahydrocannabinol (Δ^9 -THC) as the active constituent of the plant that this field caught the interest of many research groups and hundreds of papers on the chemistry, biochemistry, metabolism and clinical effects of this compound were published. However, its mechanism of action remained unknown for nearly two decades. In the mid-1980s the presence of a cannabinoid receptor in the brain was identified and shortly thereafter it was cloned. This was followed by the isolation of the major endogenous cannabinoids, anandamide and 2-arachidonoyl glycerol, and the clarification of their biosyntheses and degradations. These advances led to an avalanche of publications in a wide variety of fields. We are now in the midst of major advances in biochemistry/physiology associated with the actions of the endocannabinoids.

This short volume tries to present an up-to-date picture in some of the major fields of endocannabinoid research. The first chapter in this book, on the use of *Cannabis* in India, can be viewed as an expression of thanks to the herbal practitioners, who for centuries passed on the medical traditions associated with the drug. The chemistry chapter is a short summary of active plant, synthetic and endogenous cannabinoids being investigated today, many of which are mentioned later in the book. Cannabidiol is an unusual cannabinoid – it does not bind to the known receptors and yet exerts a variety of effects. Hence a chapter is devoted to it. Most of the remaining chapters deal with the endocannabinoid system and the endocannabinoids in a variety of conditions and physiological systems. A chapter describes the research done on Sativex[®], a standardized plant extract, shortly to be introduced in Canada as a drug for multiple sclerosis symptoms.

Numerous fields known to be affected by cannabinoids were not reviewed. The vast expanse of emotions is one of them. Most marijuana users smoke the drug in order to ‘get high’. But we know very little about the mechanisms through which cannabis affects emotions. Under certain circumstances Δ^9 -THC causes aggression, although usually it leads to sedation. Anxiety is another emotional aspect affected by cannabinoids. Although a short chapter is devoted to the calming of anxiety by cannabinoids it does not attempt to present a mechanistic picture. And we know next to nothing on the chemistry link-

ing endocannabinoids with stress, fear, love, satisfaction or despair. Are the endocannabinoids one of nature's tools to shape emotions? This is probably one of the fields which will be explored in the future. But books review the past. Possibly the next edition of this book, in 5 or 10 years time, will report on the progress made in associating endocannabinoids with emotions. Until then we shall have to remain content with more mundane topics such as neuroprotection, reproduction, appetite and effects on cancer.

The multitude of endocannabinoid effects seems like a fertile field for exploration by pharmaceutical firms. We soon expect to see the introduction of a synthetic cannabinoid antagonist in the treatment of obesity and, possibly later, drugs for neuroprotection, pain, multiple sclerosis, rheumatoid arthritis and cancer. Will post-traumatic stress disorder, schizophrenia and Tourette's syndrome come next?

Raphael Mechoulam

Jerusalem, January 2005