

Preface

Cannabis and epilepsy☆



A treatise, written in the 15th century by Ibn al-Badri, preserved as a manuscript in Paris, tells that the poet Ali ben Makki gave hashish to Zahir-ad-din Mihammed, the epileptic son of the Chamberlain of the Caliphate Council in Baghdad. Zahir had no more seizures, but had to stay on the drug ever after [1]. Actually, cannabis, in many of its forms, was previously used for centuries against seizures in India and possibly in China.

Modern research on epilepsy using plant cannabinoids started during the 1960s and 1970s. Numerous groups found that the non-psychoactive cannabidiol (CBD) [2], as well as delta-9-tetrahydrocannabinol (THC), the psychoactive constituent of cannabis, had antiepileptic properties in animals (mostly mice). In the late 1970s my group isolated nearly 400 g of pure CBD from hashish (donated by the Israeli police) and it was used in Brazil for a double-blind clinical trial, adult patients with epilepsy who were not being helped by the antiepileptic drugs used at the time. The results, published in 1980, were positive [3]. Out of 8 patients who received CBD, 3 had almost no seizures, 4 had significantly less, and only one was not improved.

Treatments based on natural products are usually first tried in small-scale trials. If the results of these trials are positive, larger clinical trials are initiated. This was the path followed in the past in the drug development of plant constituents, as well as for penicillin and cortisone. As new anti-epileptic drugs were badly needed in the 1980s, we expected that the positive effects seen with CBD would be evaluated in larger-scale clinical trials. But nothing happened for over almost 35 years.

In the early years of the present century, some parents of children with epilepsy, who were not being helped by the existing drugs, learned that CBD may be antiepileptic, tried cannabis and noting the positive effects, some of them moved to Colorado, where medical marijuana was legal and available. The therapeutic effects of cannabis varieties with high levels of CBD were reported in social media channels and these reports were presumably a major factor that made a modern, large-scale pediatric clinical trial in the US possible and approved by the FDA. Initial results from this ongoing trial are positive [4].

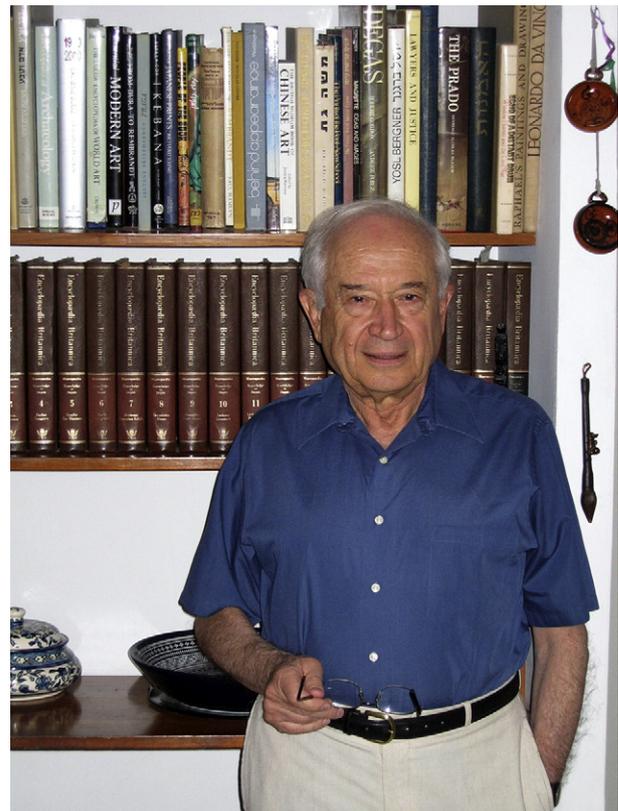
In Israel, CBD-enriched medical cannabis for intractable pediatric epilepsy is officially approved for treatment of patients and initial results are available. In a recent publication, the treatment of 74 patients (age range 1–18 years) with intractable epilepsy resistant to a large number of antiepileptic drugs was reported [5]. The formula contained CBD and THC at a ratio of 20:1 dissolved in olive oil. The CBD dose ranged from 1 to 20 mg/kg/d. The report states: “Most of the children (89%) reported reduction in seizure frequency: 13 children reported 75–100% reduction, 25 reported 50–75% reduction, 9 reported 25–50% reduction, and 19 reported <25% reduction. Five (7%) patients reported aggravation

of seizures.” Again: Did we have to wait 35 years to get and clinically apply these results?

A related aspect. Parents claim that cannabis varieties of CBD with “some THC” are more efficient than pure CBD. Are these claims being looked into? Shouldn't pure CBD be compared in patients with CBD containing minor amounts of THC?

Turning to the medical-scientific aspects of epilepsy, will the effects of CBD help us also to understand some of the yet unknown basic aspects of epilepsy? Almost 60% of cases are idiopathic. In a specific field of dermatology, the effects of CBD have been found to be (in part at least) epigenetic [6]. Is it possible that we have a related molecular/genetic cause of the effect of CBD in some epilepsies?

At present numerous groups are looking at the biochemical changes and the therapeutic effects of cannabinoids (mostly CBD) in epilepsies. Some exciting recent results in this field are reported in the present



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issue of *Epilepsy & Behavior*. These publications show that numerous aspects in the cannabinoid-epilepsy field are still to be clarified.

I expect that over the next decade we shall see major advances both in the medical-scientific and the treatment aspects of epilepsy with the help of CBD and related cannabinoids.

References

- [1] Rosenthal F. The herb hashish versus medieval Muslim society. Leiden: E. J. Brill; 1971.
- [2] Mechoulam R, Shvo Y. The structure of cannabidiol. *Tetrahedron* 1963;19:2073–8.
- [3] Cunha JM, Carlini EA, Pereira AE, Ramos OL, Pimentel G, Gagliardi R, et al. Chronic administration of CBD to healthy volunteers and epileptic patients. *Pharmacologia* 1980;21:175–85.
- [4] Devinsky O, Marsh E, Friedman D, Thiele E, Laux L, Sullivan J, et al. Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial. *Lancet Neurol* 2016;15:270–8.
- [5] Tzadok M, Uliel-Siboni S, Linder I, Kramer U, Epstein O, Menascu S, et al. CBD-enriched medical cannabis for intractable pediatric epilepsy: the current Israeli experience. *Seizure* 2016;35:41–4.
- [6] Pucci M, Rapino C, Di Francesco A, Dainese E, D'Addario C, Maccarrone M. Epigenetic control of skin differentiation genes by phytocannabinoids. *Br J Pharmacol* 2013;170: 581–91.

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