

## Chapter 2

THERAPEUTIC POTENTIAL OF CANNABINOIDS IN  
NEUROLOGICAL DISORDERS\*†

Paul Consroe and Stuart R. Snider

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† Abbreviations: AGS = audiogenic seizure; CBD = cannabidiol; ED<sub>50</sub> = median effective dose; EEG = electroencephalogram; ESM = ethosuximide; EST = minimal electroshock seizure threshold; GABA = gamma-aminobutyric acid; LD<sub>50</sub> = median lethal dose; MES = maximal electroshock seizure; MEST = MES threshold; PI = protective index (TD<sub>50</sub>/ED<sub>50</sub>); PTZ = pentylenetetrazol; PB = phenobarbital; PHT = phenytoin; TD<sub>50</sub> = median toxic dose; THC = tetrahydrocannabinol; TMD = trimethadione.

## I. INTRODUCTION

Marijuana (*Cannabis sativa* L.) has been used for fiber, food, recreation and medicine for thousands of years. Medicinal marijuana, like hedonic marijuana, has progressed from empirical use and anecdotal reports to the more critical scrutiny of modern scientific investigation. The antiquity and diversity of traditional folk-medical uses of marijuana have been described in several representative publications.<sup>1-3</sup> The marijuana potions and nostrums used throughout the ages were characterized by wide differences in potency and effects. This is because of the complexity and variability of active constituents of the plant itself and the different methods of preparation and coadmixture with other active substances that have been used. Hence, it is not surprising that the early literature is replete with reports of the inconsistent or contradictory effects of marijuana preparations. Nevertheless, the historical accounts of the properties of marijuana have provided an impetus for modern investigations on the effects and potential therapeutic uses of marijuana, its constituents, and their analogs.

For many reasons, marijuana per se is not a good candidate for therapeutic application. Its potential for causing unpleasant and sometimes alarming reactions has been known for a long time.<sup>1,2</sup> It is difficult to obtain uniform and reliable preparations and dosage forms of marijuana and, therefore, to evaluate its safety and efficacy, because the plant contains over 421 compounds in varying proportions<sup>4</sup> and most of these have never been pharmacologically evaluated. While marijuana, like other botanicals, lacks the specificity of action of many new therapeutic agents, some of its natural constituents or their synthetic homologs may prove to be therapeutically important.  $\Delta^9$ -Tetrahydrocannabinol ( $\Delta^9$ -THC), the major psychoactive cannabinoid of marijuana, has been used experimentally for glaucoma and for vomiting caused by anticancer drugs, as have the synthetic cannabinomimetic analogs, nabilone, levonantradol, nabilan, and naboctate.<sup>5</sup>  $\Delta^9$ -THC has also been evaluated for its antispasmodic and antitremor effects in patients with multiple sclerosis.<sup>6,7</sup> Additionally, cannabidiol (CBD), a major nonpsychoactive ingredient of marijuana, has been tried experimentally for epilepsy<sup>8</sup> and, more recently, dystonia.<sup>9</sup>

At the preclinical level, much progress has been made in defining the complex neurobehavioral effects of cannabinoids. In large measure, this research has provided the basis for use of CBD in some types of human seizure disorders. Testing clinical efficacy and safety of a new drug to be used as chronic therapy in neurological disorders is methodologically difficult, time consuming, and expensive. These problems, in conjunction with regulatory constraints of cannabinoid procurement and usage, may explain why clinical studies of the effects of cannabinoids in epilepsy, multiple sclerosis, dystonia, and other movement disorders are limited and incomplete at the present time.

Within the past several years, therapeutic aspects of marijuana and related cannabinoids have been the theme of two published symposia<sup>10,11</sup> and several general reviews.<sup>5,12-14</sup> The purpose of the present treatise is to review and update the research and potential applications of cannabinoids in epilepsy and other neurological disorders.

## II. CANNABINOIDS AND SEIZURE DISORDERS

### A. Overview of Seizure Disorders

A seizure is a paroxysmal event that consists of a transient distortion of normal electrical activity in the brain and some alteration of normal motor, sensory, autonomic, or psychic function. Recurrent seizures are characteristic of idiopathic or primary epilepsy, and may occur in symptomatic or secondary epilepsy, a diverse group

of chronic or progressive neurological disorders. Epilepsy is of great sociomedical importance. It is one of the most prevalent neurological disorders: about 1% of the population are affected.<sup>15</sup> It tends to last for life, and it may have profound medical, economic, social, and legal consequences for the afflicted individual.

Classification of epileptic seizures is based upon the clinical manifestations of the attack and pattern of the electroencephalogram (EEG).<sup>16</sup> In the international classification, the major headings are partial seizures (those that originate in and are largely restricted to one region or focus of cerebral tissue) and generalized seizures (those that involve diffuse, usually bilateral, areas of brain). The former are commonly occurring and are subtyped simple partial (cortical focal) and complex partial (temporal lobe or psychomotor) seizures. Some of the common types of the primary generalized seizures are grand mal (tonic-clonic and clonic-tonic-clonic), myoclonic, and absence (petit mal) seizures. Mixed seizure types may also be present at the beginning or evolve during the course of the illness. One example of common occurrence is when partial seizures generalize secondarily to involve the added feature of grand mal convulsions.<sup>17</sup>

Symptomatic epilepsy may result from head trauma, neoplasm, cerebral vascular disorders, infection, metabolic derangements and, in young children, high fever. In many cases of idiopathic epilepsy, although no specific cause can be identified, it is clear that genetic factors contribute to the etiology and pathology.<sup>17</sup>

While the molecular bases of epileptogenicity are still unknown, there is evidence that abnormalities of central neurotransmitters may be involved. Impaired gamma-aminobutyric acid (GABA)-mediated inhibition is thought to be involved in partial seizures and generalized seizures of the grand mal type.<sup>18</sup> Other imbalances of neurotransmitter-mediated inhibition and/or excitation also may play a role in the pathogenesis of the epilepsies. These include deficient neurotransmission or function of taurine, norepinephrine, and serotonin, and/or excessive neurotransmission or function of aspartate and glutamate.<sup>19,20</sup>

Antiepileptic drugs are of unquestionable value in the symptomatic treatment of epilepsy, and it is generally assumed that certain of these are selective for particular types of seizures. Interestingly, a recent comprehensive review of controlled clinical trials of antiepileptic drugs concluded that there was no firm indication of which drug is more suitable for which seizure type.<sup>21</sup> Nevertheless, comparative clinical trials together with many years of drug experience have provided general therapeutic guidelines for different seizure types. Phenytoin (PHT), phenobarbital (PB), carbamazepine, and primidone are the four primary drugs used to treat partial epilepsies.<sup>17,22</sup> These same drugs (especially PHT or carbamazepine) are commonly used to treat primary generalized seizures of the grand mal type,<sup>22</sup> although valproic acid has been recommended as a first choice.<sup>17</sup> Ethosuximide (ESM) is generally considered the first choice for generalized absence seizures,<sup>17,22</sup> but valproic acid and clonazepam also are effective in many cases.<sup>22</sup> These drugs have supplanted trimethadione (TMD), a drug used widely in the past to treat absence seizures. Valproic acid is also used to treat some forms of generalized myoclonic seizures.<sup>22</sup>

While antiepileptic drugs are the mainstay of seizure treatment, there are some problems and limitations associated with their use. They may have to be taken for life and, in many patients, it may be difficult to achieve effective long-term control of seizures, lack of drug toxicity, or a combination of both. It has been estimated that 20 to 30% of epileptics are not adequately controlled with currently available drugs, even when they are used in combinations and monitored by blood serum determinations.<sup>23</sup> In general, effective control of seizures is achieved less often in patients with complex partial seizures, partial seizures that secondarily generalize to grand mal convulsions, and myoclonic seizures.<sup>17,22,23</sup> Additionally, untoward effects on arousal, motor per-

formance, mood, and other body functions may occur with virtually all existing antiepileptic drugs.<sup>17</sup>

In spite of the need for new therapy of epilepsy, there has been little recent progress in the introduction of new or novel antiepileptic drugs into clinical practice.<sup>24</sup> Only three new drugs (carbamazepine, clonazepam, and valproic acid) have been marketed in the U.S. since 1960, and few pharmaceutical firms today are interested in antiepileptic drug development. A major reason for the latter is financial; i.e., the cost of new drug development far exceeds the expected monetary return from commercial marketing.<sup>24</sup> Federal support (e.g., from the Epilepsy Branch of the National Institute on Neurological and Communicative Disorders and Stroke) has been available, but represents only a small portion of the resources needed to bring a new drug to the market.<sup>24</sup>

Despite these problems and concerns, preclinical evaluation of new antiepileptic drugs has continued. Cannabinoids have been identified as novel types of anticonvulsant drugs, and currently the most promising is CBD. CBD has potent anticonvulsant activity, minimal neurotoxicity, and none of the (human) psychoactivity that is typical of  $\Delta^9$ -THC. In the following sections, the experimental and clinical literature on the effects of CBD, marijuana, and other cannabinoids on seizures is reviewed.

## B. Cannabinoids and Seizure Activity in Laboratory Animals

It has been clearly documented that cannabinoids can induce<sup>25,26</sup> or suppress<sup>5,12,25-29</sup> the behavioral and EEG manifestations of seizures in laboratory animals. In some cases, both of these actions have been observed within the same experimental paradigm. The electrophysiological basis for these paradoxical behavioral effects has been detailed previously.<sup>26,27,30</sup> The following discussion will attempt to summarize and update the experimental literature on cannabinoids and seizure activity.

### 1. Convulsant Effects and Mechanisms

Convulsions subsequent to cannabinoid administration have been reported to occur under certain conditions in "normal" (nonseizure-susceptible) animals, genetically seizure-susceptible animals, and experimentally seizure-susceptible animals.

#### a. Normal Animals

$\Delta^9$ -THC, given by intravenous (i.v.), oral and inhalational routes, has been reported to cause convulsant activity in normal (i.e., nonseizure-susceptible) rats, dogs, and monkeys.<sup>25</sup> These generalized body twitches, involuntary jumping or "popcorn" convulsions, clonic convulsions and/or clonic-tonic convulsions occurred only with lethal or near-lethal doses given acutely or high doses given repeatedly for months, and occurred only in some of the animals so treated.<sup>25</sup> CBD, given in single i.v. doses within the lethal range, also has been reported to cause convulsions in normal rats<sup>31</sup> and monkeys.<sup>31,32</sup> The LD<sub>50</sub>s of i.v. CBD were about six times higher in the rat and about two times higher in the monkey than were those of i.v.  $\Delta^9$ -THC.<sup>31</sup> The incidence of convulsions with i.v. CBD, like that of  $\Delta^9$ -THC, was variable, and some animals died of cardiorespiratory arrest without first exhibiting a convulsion. Further, 90-day oral treatment of monkeys with CBD, given in doses below and above the i.v. LD<sub>50</sub>, did not evince convulsions or, for that matter, any other behavioral abnormality.<sup>32</sup>

Cannabinoids of the THC type produce a number of central excitatory effects that have been postulated to be related to the convulsant activity of these compounds.<sup>26,30</sup> These include production of hypersynchronous EEG activity, and enhancement of electrically caused cortical potentials, auditory-evoked cortical responses, photically evoked cortical afterdischarges, and electrically evoked spinal potentials. These effects, except for hypersynchronous EEG activity, have been described only in normal ani-

mals. They occur at cannabinoid doses that are 50 to 100 times lower than those required for the production of convulsions in these animals.

Hypersynchronous EEG activity has been recorded from cortical and subcortical sites in many species.<sup>25,26,30,33-35</sup> This activity has been described as spindle-like activity, spikes and waves, polyspikes, and epileptiform-like activity.<sup>25,26</sup> The high-voltage EEG patterns produced by  $\Delta^9$ -THC have some resemblance to the spindles of slow-wave sleep but power spectral analysis has shown them to be unique and unrelated to normal sleep-spindles.<sup>35</sup> Hypersynchronous EEG activity has been produced by marijuana,  $\Delta^9$ -THC and THC analogs when given over a wide range of doses and dosing schedules, and when given by both peripheral and central routes of administration.<sup>25,34</sup> In contrast, CBD was inactive when given peripherally,<sup>25,26</sup> and only weakly active when given intracerebrally.<sup>34</sup> This type of EEG activity was usually correlated with behavioral hypoactivity or immobility and seldom with clonic or tonic-clonic convulsions.<sup>25,26,34,35</sup>

$\Delta^9$ -THC also has been shown to enhance a variety of experimentally evoked responses in cortex and spinal cord. In unanesthetized, artificially respired monkeys, surgically sectioned at the mesencephalic, pontine, or cervical spinal level,  $\Delta^9$ -THC enhanced electrically evoked responses in cortex at low doses, and decreased them at higher doses.<sup>36</sup> In this preparation, the excitatory effect of  $\Delta^9$ -THC resembled that of subconvulsant doses of picrotoxin or pentylenetetrazol (PTZ).<sup>37,38</sup> In conscious unrestrained rats,  $\Delta^9$ -THC increased the amplitude of the transcollosal cortical evoked response at low doses and decreased it at higher doses.<sup>39</sup> PTZ in subconvulsant doses and PHT in anticonvulsant doses also increased the electrically evoked cortical response, whereas ESM and CBD in both low and high (anticonvulsant) doses caused only depression of the response.<sup>39</sup>

In conscious restrained cats,  $\Delta^9$ -THC enhanced auditory-evoked cortical potentials, and caused prominent spikes on the cortical EEG.<sup>40</sup> The reference drugs of this study — mescaline and pentobarbital — also enhanced the cortical potentials, but did not produce EEG spikes.<sup>40</sup> In conscious restrained rats,  $\Delta^9$ -THC (in an anticonvulsant dose) and PTZ (in subconvulsant doses) each increased photically evoked cortical afterdischarges.<sup>41</sup> In contrast, TMD and ESM depressed, and PHT and CBD did not affect, photically induced cortical afterdischarges in this preparation.<sup>41</sup>

Finally, in unanesthetized spinal cats, low doses of  $\Delta^9$ -THC increased pre- and post-tetanic potentials of spinal motor neurons.<sup>42</sup> In contrast to these excitatory effects, higher doses of  $\Delta^9$ -THC and a wide range of doses of CBD and PHT caused depression of these potentials.<sup>42</sup> In a related study using this preparation,  $\Delta^9$ -THC increased the amplitude of the excitatory postsynaptic potentials and decreased the amplitude of the inhibitory postsynaptic potentials.<sup>43</sup> The cannabinoid also caused depression as evidenced by a rise in the firing threshold for the motoneuron action potential.<sup>43</sup> The combined data obtained from these spinal cord and brain studies suggest that cannabinoids can influence neurotransmission and that the synapse is a sensitive target for their action.

#### *b. Genetically Seizure-Susceptible Animals*

Cannabinoid-produced convulsions can occur in some stocks of animals that have a genetic predisposition to seizures or a specific genetic predisposition to the convulsant effects of cannabinoids. Generally, these convulsions result from the administration of relatively low and otherwise nontoxic doses of  $\Delta^9$ -THC and THC-like compounds. Convulsions do not occur with CBD and other nonpsychoactive cannabinoids, even in doses appreciably higher than those of  $\Delta^9$ -THC.

One of these stocks is the epileptic beagle dog that has behavioral seizures — immobility, various automatisms, generalized clonic-tonic convulsions — and interictal

focal spiking in the amygdala.<sup>26,44,45</sup> Although convulsions occur spontaneously, their occurrence is highly variable and unpredictable.<sup>45</sup> Commonly employed induction techniques to trigger convulsions in these dogs have been ineffective.<sup>45</sup> Canine epilepsy appears to be transmitted by an autosomal recessive gene that is associated with a sex-linked suppressor on the X chromosome.<sup>45</sup> Because of this, there is a higher incidence of seizures in males.<sup>45</sup> In male epileptic beagle dogs, a single oral dose (5 mg/kg) of  $\Delta^9$ -THC evoked myoclonus and an exacerbation of EEG focal activity in the amygdala.<sup>26,44</sup> Myoclonus also occurred after 9 to 19 daily doses (3 to 5 mg/kg, orally) of  $\Delta^9$ -THC, suggesting a lack of tolerance to this effect. Additionally,  $\Delta^9$ -THC caused increased frequency of clonic-tonic convulsions in some of the dogs after chronic dosing. However, CBD given in (acute or chronic) oral doses equivalent to those of  $\Delta^9$ -THC did not precipitate any convulsive activity in these animals.<sup>44</sup>

Another stock is the THC-seizure-susceptible rabbit.<sup>25,28,33,46</sup> Convulsions in these rabbits have never been observed to arise spontaneously or after environmental stimuli that are known to trigger convulsions in some other genetically seizure-susceptible animals.<sup>25</sup> However, immediately following the acute i.v. administration of  $\Delta^9$ -THC or other THC analogs, the animals developed tonic and clonic limb movements, nystagmus, thrashing, and headtuck.<sup>25,33,46</sup> Convulsive activity occurred over a wide dose range of  $\Delta^9$ -THC, with the minimally effective convulsant dose being 0.05 mg/kg.<sup>33</sup> Following daily administration of  $\Delta^9$ -THC, a (reversible) tolerance to the convulsant effect occurred.<sup>33</sup> CBD and other nonpsychoactive cannabinoids at acute (i.v.) doses of up to 20 mg/kg,<sup>28,46</sup> and several noncannabinoid, psychoactive drugs in behaviorally active doses,<sup>33</sup> failed to cause convulsions. Mechanistically, THC-seizure susceptibility was shown to be due to the homozygous expression of a single autosomal recessive gene that was not sex-linked.<sup>33</sup>

Additionally, the Swiss-Webster mouse is another stock that is sensitive to the convulsant effects of cannabinoids.<sup>47,48</sup> These genetically heterogeneous mice normally exhibit a variable incidence of handling-induced convulsions, i.e., tonic or tonic-clonic convulsions, when they are gently picked up by the tail and, if necessary, spun gently through 180°.<sup>49</sup> This same variability also occurs across inbred strains of mice, which suggests that there is a genetic predisposition to this type of convulsion.<sup>49</sup> However, the mode of inheritance of seizure susceptibility is unknown. The incidence of handling-induced convulsion in genetically heterogeneous stocks can be increased under some experimental conditions such as during ethanol withdrawal following forced ethanol dependence. Using this latter paradigm 10 to 40 mg/kg of  $\Delta^9$ -THC given intraperitoneally (i.p.), and the synthetic THC-like cannabinoid, nabilone (2.5 to 10 mg/kg, i.p.) were shown to enhance the severity of convulsion.<sup>47</sup> Further,  $\Delta^9$ -THC (10 to 80 mg/kg, i.p.), nabilone (5 to 20 mg/kg, i.p.), and cannabitol (80 mg/kg, i.p.) each produced handling-induced convulsions in control, otherwise untreated, Swiss-Webster mice.<sup>48</sup> The duration of the  $\Delta^9$ -THC-produced convulsion was dose related, although there were wide variations in the responses of the mice to the cannabinoid. These handling-induced convulsions were not observed in other groups of Swiss-Webster mice following vehicle or CBD (80 mg/kg, i.p.) administrations.<sup>48</sup> Additionally, tolerance developed to the convulsant effects of  $\Delta^9$ -THC when it was given on 2 consecutive days.<sup>48</sup>

### *c. Experimentally Seizure-Susceptible Animals*

Convulsions subsequent to relatively low-dose administration of cannabinoids can occur in animals rendered seizure susceptible by some experimental techniques.<sup>26,30,44,50-55</sup> One technique involved the i.v. administration of a large, albeit subconvulsant, dose (750,000 units/kg) of sodium penicillin to mongrel dogs.<sup>50</sup> Acute marijuana smoking by these dogs produced a spike and wave pattern on the cortical EEG

and associated muscular jerks. Chronic marijuana smoking produced an EEG pattern of spike and wave complexes and polyspike bursts, and elicited grand mal convulsions in some of the dogs. By themselves the doses of marijuana and penicillin used in this experiment did not produce any major effects on gross behaviour or on the EEG.<sup>50</sup>

Other techniques involved implantation or injection of cobalt, iron, or aluminum into the cortex of animals to produce an epileptic focus. This results in a gradual development of EEG seizures which are localized to the focus but may generalize to other parts of the brain. The EEG seizures may diminish with time in the cobalt and aluminum preparations. In the iron preparation they may be manifested, more or less, continually. These experimental animals exhibit brief, usually infrequent behavioral convulsions consisting of clonic or clonic-tonic movements of the limbs and facial muscles. The effects of cannabinoids in these epileptic animals are complex and depend on the preparation, the cannabinoid and dose administered, and the dosing schedule employed.

In iron-induced epileptic rats,<sup>51</sup>  $\Delta^9$ -THC, given in acute doses of 1 to 6 mg/kg (i.p.), precipitated intermittent episodes of clonic convulsions in all the animals and, paradoxically, decreased the frequency of paroxysmal EEG discharges from the iron foci. Higher acute doses (15 mg/kg) of the cannabinoid produced epileptiform-like (polyspike) afterdischarges at both focal and contralateral recording sites. The pharmacological effects of two THC metabolites and of CBD and PTZ were also ascertained in this preparation. 11-Hydroxy- $\Delta^9$ -THC did not precipitate convulsions but did elicit the same EEG effects as  $\Delta^9$ -THC. 8-Beta-hydroxy- $\Delta^9$ -THC and PTZ each evoked the EEG polyspikes and convulsions, but did not depress or enhance the epileptic foci. Finally, CBD was devoid of behavioral and EEG effects even in doses up to 100 mg/kg (i.p.).

In cobalt-induced epileptic rats,<sup>52</sup> acute administration of  $\Delta^9$ -THC, 0.5 to 100 mg/kg (i.p.), produced a dose-related increase in the frequency of focal potentials, and caused generalized bursts of polyspikes. In some (but not all) of these rats,  $\Delta^9$ -THC also precipitated or exacerbated clonic convulsions. 11-Hydroxy- $\Delta^9$ -THC produced bursts of polyspikes, but did not affect the focal potentials and did not elicit any convulsions. CBD (1 to 200 mg/kg) did not affect the focal potentials and did not produce polyspikes or convulsions; however, it did abolish clonic convulsions in the rats who were manifesting this activity. Additionally, the reference anticonvulsant drugs ESM, TMD, and PHT, and the convulsant drug PTZ were also studied. ESM and TMD each suppressed the focal potentials, whereas PHT had no effect on this measure. (The effects of these anticonvulsants on motor seizures were not analyzed because of insufficient data.) Finally, PTZ (given in subconvulsant doses) did not affect the focal potentials, but did produce polyspikes similar to those of  $\Delta^9$ -THC.

The effects of cannabinoids following repeated (i.p.) dosing have also been ascertained in cobalt-induced epileptic rats.<sup>53</sup>  $\Delta^9$ -THC (10 mg/kg),  $\Delta^8$ -THC (10 mg/kg), or CBD (60 mg/kg) was administered twice daily for 4 days after cobalt implantation. Both THC compounds initially (days 1 and 2 of treatment) reduced or abolished EEG (repetitive, bilaterally hypersynchronous spike activity) and behavioral (bilateral, clonic, and tonic movements of forelimbs and of facial muscles) manifestations of the spontaneous, generalized seizures. During this period, however, spontaneous focal activity (spikes and spike and wave complexes) and concomitant unilateral clonic movements (of forelimb and facial muscles) were prolonged by  $\Delta^9$ -THC or  $\Delta^8$ -THC. By the third treatment day, tolerance developed to the anticonvulsant effect of the THC compounds on the generalized seizures. Additionally, CBD had no effects on any of the EEG or behavioral manifestations of seizures in these animals.

In cats with alumina cream foci in a quiescent stage, acute  $\Delta^9$ -THC (1.5 mg/kg, orally) reactivated focal discharges on the cortical EEG.<sup>26</sup> The  $\Delta^9$ -THC-evoked focal activity was accompanied by localized somesthetic sensation consisting of facial

scratching. In this preparation (like the cobalt paradigm), it appears that activation of a preexisting cortical focus by  $\Delta^9$ -THC may be responsible for the behavioral manifestations of seizures.<sup>26</sup>

Another technique involved the repetitive electrical stimulation of limbic structures, i.e., kindled limbic seizures. This results in a gradual development of focal EEG seizures and convulsions (e.g., jaw and limb clonus). The seizure afterdischarges, assessed in terms of threshold, amplitude, and duration, may be measured at the focal site of electrical stimulation and at distant sites in the brain, the latter being an indication of the spread of seizures.

In conscious unrestrained rats, acute  $\Delta^9$ -THC increased the duration of afterdischarges, bilaterally, in frontal cortices and dorsal hippocampi following kindling of the left subiculum.<sup>54</sup> The behavioral consequence of this effect was purported to be an increase in the duration of the convulsion.<sup>55</sup> However, acute  $\Delta^9$ -THC also elevated the threshold for convulsions and for production of afterdischarges at the focal site of stimulation.<sup>54</sup> Acute CBD, PHT, and ESM each displayed mainly anticonvulsant effects and generally depressed paroxysmal activity at the limbic focus.<sup>54</sup>

In amygdaloid-kindled rats, acute  $\Delta^9$ -THC (45 mg/kg, i.p.) suppressed the kindled seizures, and tolerance to this effect occurred during repeated dosing (six injections of  $\Delta^9$ -THC given every other day).<sup>56</sup> However, a dramatic increase in the duration of clonic convulsions occurred for several days following the last administration of  $\Delta^9$ -THC. This suggests that withdrawal of  $\Delta^9$ -THC following its short-term administration may exacerbate seizures in some epileptic models.

The withdrawal effects of  $\Delta^9$ -THC and other drugs have been studied in other convulsant models. In normal mice,  $\Delta^9$ -THC caused a withdrawal hyperexcitability (as measured by 6- and 60-Hz minimal electroshock seizure threshold tests) following daily administration (100 mg/kg, i.p.) for 2 days.<sup>57</sup> A withdrawal hyperexcitability (on maximal electroshock threshold and 60-Hz minimal electroshock threshold tests) was also seen following 3 days of PB treatment.<sup>57</sup> However, neither PHT nor CBD (120 mg/kg, i.p., daily for 3 days) caused this effect.<sup>57</sup> In a subsequent and related study in normal mice, the effects of  $\Delta^9$ -THC (100 mg/kg, i.p.), CBD (120 mg/kg, i.p.), and PHT, each given daily for 22 days, were ascertained in the same electroshock seizure tests.<sup>58</sup> In contrast to the subacute administrations cited above, this longer-term administration of  $\Delta^9$ -THC (or the other drugs) did not result in a withdrawal hyperexcitability in any of the tests.<sup>58</sup> Additionally, withdrawal from marijuana, following 11, 13, or 28 days of oral administration of crude marijuana extract to normal mice, did not alter the threshold to convulsions produced by the convulsant drug PTZ.<sup>59</sup>

#### *d. Summary*

Cannabinoids can produce convulsions in laboratory animals under three general conditions. First, lethal or near-lethal doses of  $\Delta^9$ -THC, related THC compounds, and CBD may cause convulsions in normal, nonseizure-susceptible rodents, dogs, and/or monkeys. CBD is much less potent than  $\Delta^9$ -THC in causing these convulsions, and the latter do not invariably occur in all animals given either cannabinoid, even in lethal doses. Second, convulsions can be induced in genetically seizure-susceptible animals, the epileptic beagle dog, the THC-seizure-susceptible rabbit and the genetically heterogenous Swiss-Webster mouse with low doses of THC compounds, but not with similar or higher doses of CBD. Third, convulsions can be induced by cannabinoids in the iron- or cobalt-induced epileptic rat, the aluminum-induced epileptic cat, and the limbic-kindled epileptic rat. In these experimentally produced models of epilepsy, low doses of  $\Delta^9$ -THC and some THC compounds can elicit convulsions. Similar or higher doses of CBD do not cause convulsions. Additionally, withdrawal of  $\Delta^9$ -THC after

repeated high-dose administration might increase seizure susceptibility in epileptic animals, but more information is needed on this important point.

The convulsant effects of THC cannabinoids may be related to central nervous stimulation since these compounds enhance activity in experimentally induced seizure foci and enhance spread of paroxysmal activity from such foci. Additionally,  $\Delta^9$ -THC has been reported to enhance electrically, audiogenically, and photically caused neuronal excitability and produce hypersynchrony of the EEG. Excitation of the cortical seizure focus in the rat cobalt model and cat aluminum model and of the amygdala focus in the epileptic beagle dog appears to be causally related to behavioral seizures. However, in the rat iron model there does not appear to be a relationship of the (dose-related) depression of the cortical focus by the  $\Delta^9$ -THC and the convulsant effect of the cannabinoid. Enhancement of seizure spread and prolongation of afterdischarges at focal and nonfocal sites in limbic kindled rats appears to be causally related to behavioral seizures. In this preparation, as in many others,  $\Delta^9$ -THC also produces depressant or anticonvulsant effects as well as stimulatory effects. Further, direct correlations between other cannabinoid-produced excitatory effects and convulsions have yet to be established.

## 2. Anticonvulsant Effects and Mechanisms

One of the most consistent effects of cannabinoids is the prevention or blockade of convulsions. It has been demonstrated in a wide variety of seizure models in rats, mice, frogs, chickens, rabbits, cats, and baboons.<sup>5,12,25-29</sup> Anticonvulsant activity has been observed with both THC and CBD types of cannabinoids, and usually in typical dose-response fashion.<sup>5,12,28,29</sup> A summary of some of the anticonvulsant and potential mechanistic effects of cannabinoids is presented below. These effects are included under the general headings of the experimental seizure type or model that has been used. This classification appears to have practical and heuristic value since many of these seizure paradigms can predict the potential clinical utility and presumed action of anticonvulsant drugs in human epilepsy.<sup>60</sup>

### a. Maximal (Tonic) and Minimal (Clonic) Generalized Seizures

Maximal (tonic) and minimal (clonic) generalized seizures can be induced by a variety of techniques involving electrical stimulation (usually via corneal electrodes) and peripheral (systemic) administration of convulsant drugs. In general, differential antagonism against tonic or clonic seizures correlates with the clinical efficacy and (presumed) mechanism of action of anticonvulsant drugs.<sup>60,61</sup> While maximal electroshock seizure (MES) and minimal PTZ seizure models in rodents are used most commonly, the qualitative effects of anticonvulsant drugs are considered to be largely independent of the means used to evoke the seizures, and the animal species used.<sup>61</sup> In general, maximal seizure models are more sensitive to antiepileptic drugs (e.g., PHT, PB, and carbamazepine) that are clinically effective against generalized grand mal seizures and partial seizures, whereas minimal seizure models are more sensitive to anti-epileptic drugs (e.g., ESM, TMD) that are clinically effective against generalized absence seizures.<sup>60,61</sup> Furthermore, a traditional view is that blockade of maximal and minimal seizures by anticonvulsant drugs is related to reduction of the spread of a seizure discharge and elevation of the threshold of a seizure discharge, respectively.<sup>60,61</sup>

In electroshock-seizure models  $\Delta^9$ -THC and CBD, given acutely, block maximal seizures rather consistently, but their acute effects on minimal seizures are more variable.<sup>25,27,28,62</sup>  $\Delta^9$ -THC and CBD each blocked MES in mice, rats, and frogs, and also elevated maximal electroshock seizure threshold (MEST) in mice.<sup>25,27,29</sup> In mice, both drugs elevated (minimal) 6-Hz electroshock seizure threshold (EST), but  $\Delta^9$ -THC lowered, and CBD had no effect on, (minimal) 60-Hz EST.<sup>27,29</sup> Comparison of effects of

these cannabinoids and antiepileptic drugs (PHT, ESM, and PB) in mice indicated that the acute anticonvulsant profiles of CBD and PHT were most similar.<sup>27,29</sup>

Anti-MES activity is also characteristic of other cannabinoids given acutely. These include other marijuana constituents ( $\Delta^8$ -THC, cannabinalol, and  $\Delta^9$ -THC acids),<sup>27,29</sup> various THC metabolites (11-hydroxy- $\Delta^9$ -THC, 8-beta-hydroxy- $\Delta^9$ -THC, and 8-alpha, 11-dihydroxy- $\Delta^9$ -THC),<sup>27,29</sup> and a variety of synthetic analogs of THC (e.g., 9-nor- $\Delta^8$ -THC and 1, 2-dimethylheptyl isomers of  $\Delta^6$ - $\Delta^{10}$ -THC),<sup>5,27,29</sup> cannabinalol (9-nor-9-alpha-hydroxy-hexahydro-cannabinalol and 9-nor-9-beta-hydroxy-hexahydro-cannabinalol),<sup>27,29</sup> and CBD.<sup>62,63</sup> In the CBD series, several analogs were active including those with oxygen functions on the terpenoid ring, those with a 1, 2-dimethylheptyl side chain on the resorcinol moiety, and the unnatural (+) isomer of CBD.<sup>62,63</sup> Interestingly, (+)-CBD appeared to be equiactive to that of the naturally occurring (-)-CBD in blocking MES and prolonging pentobarbital-induced sleep time of mice.<sup>63</sup> Further, the 1, 2-dimethylheptyl analogs of (+)-CBD and (-)-CBD appeared to have somewhat greater activity than those of their parent homologs in both tests.<sup>63</sup>

The acute potencies of cannabinoids and antiepileptic drugs for blocking MES as well as for producing differential neurotoxicity (as usually measured by the rotarod test) are highly dependent on the species (e.g., mouse, rat, or frog) and route of administration (i.p., i.v., or oral) used.<sup>27-29,64</sup> Because of this, wide variations in the anticonvulsant  $ED_{50}$ s, neurotoxic  $TD_{50}$ s and protective indexes ( $PIs = TD_{50}/ED_{50}$ ) of drugs, especially  $\Delta^9$ -THC and CBD, have been reported.<sup>27-29</sup> However, a most consistent finding across studies is that CBD has a PI greater than unity, and thus has a greater selectivity of anticonvulsant action relative to neurotoxicity.<sup>25,27-29,64</sup> Furthermore, the PI (or margin of safety) of CBD consistently has been shown to be comparable to that of one or more of the antiepileptic drugs (PB, PHT, and carbamazepine) that are clinically effective against generalized grand mal seizures and partial seizures.<sup>25,27-29,64</sup>

The effects of repeated cannabinoid administration in electroshock seizure models are characterized by tolerance to maximal seizure blockade and both tolerance and reverse-tolerance to minimal seizure blockade. Following 3 days of treatment, tolerance developed to the anti-MES effects of  $\Delta^9$ -THC, CBD, and PHT in mice.<sup>57</sup> Following 22 days of treatment with  $\Delta^9$ -THC, CBD, or PHT in mice, anticonvulsant tolerance also occurred in the MEST test.<sup>58</sup> However, the influence of 22-day treatment on minimal seizures depended upon the drug and specific test employed.<sup>58</sup> With  $\Delta^9$ -THC, tolerance occurred to its anticonvulsant effects in the 6-Hz-EST test and to its excitatory effects in the 60-Hz-EST test. With CBD, there was a progressive increase in sensitivity in both EST tests, i.e., an anticonvulsant reverse-tolerance. Finally with PHT, the magnitude of its anticonvulsant effect in the 6-Hz-EST test remained unchanged, but (like CBD) an anticonvulsant reverse-tolerance occurred in the 60-Hz-EST test.

In most chemoshock-induced seizure models, there is a trend for acute cannabinoids to block the endpoint of maximal convulsion.<sup>25,28</sup> The seizure endpoint of minimal convulsion and lethality are usually not prevented by acute CBD and  $\Delta^9$ -THC, or are exacerbated by acute  $\Delta^9$ -THC.<sup>25,28</sup> There are, however, exceptions to these generalizations. Some of these depend on the method of seizure assessment or on the specific convulsant drug used.

PTZ-induced seizures in rats and mice have been used most commonly. With acute  $\Delta^9$ -THC, most studies showed a partial reduction in the incidence of tonic convulsion, and no change or enhancement in the incidence of clonic convulsion and lethality.<sup>25</sup> Generally, these effects resembled those of the antiepileptic drug PHT.<sup>29</sup> Additionally, other studies in mice have demonstrated that acute  $\Delta^9$ -THC,  $\Delta^8$ -THC, and several THC metabolites (11-hydroxy- $\Delta^8$ -THC, 11-oxo- $\Delta^8$ -THC, and epoxyhexahydro-cannabinalol metabolites of  $\Delta^8$ -THC) delayed the latencies to tonic and clonic convulsions produced

by PTZ.<sup>65,66</sup> The incidences of PTZ-produced tonic convulsion and lethality were also reduced, and the metabolites were more potent for all effects than their parent compounds.<sup>65,66</sup> These findings, in conjunction with other findings in the mouse MES test,<sup>27,29</sup> may suggest the potential importance of some metabolites in the anticonvulsant activity of the THC. With acute CBD, most studies have shown dose-related protection against tonic convulsions but no protection against clonic convulsion or lethality caused by PTZ.<sup>28</sup> CBD, unlike THC, did not enhance the convulsant or lethal effects of PTZ.<sup>28</sup>

A variety of other seizure models in rats or mice have been used to assess the acute effects of  $\Delta^9$ -THC. No protection occurred against lidocaine-induced clonus and lethality,<sup>25</sup> picrotoxin-induced clonus and lethality,<sup>25</sup> or nicotine-induced tonus and lethality.<sup>67</sup> Also, strychnine-induced tonic-clonic convulsions and lethality were unaffected<sup>25</sup> or enhanced<sup>67</sup> by  $\Delta^9$ -THC.

Additionally, the acute effects of CBD have been assessed in mice against seizures and lethality produced by several convulsant drugs.<sup>68</sup> These were the GABA inhibitors 3-mercaptopropionic acid, isonicotinic acid hydrazide, bicuculline, picrotoxin, and PTZ, and the glycine antagonist strychnine. CBD produced dose-dependent protection against tonic convulsions of all the drugs except strychnine. CBD also prevented lethality caused by 3-mercaptopropionic acid, but failed to prevent lethality of the other convulsive drugs. Furthermore, CBD failed to prevent clonic convulsions of all the convulsant drugs.

#### *b. Genetically Dependent Seizures*

Genetically seizure-susceptible animals have provided a valuable resource for the study of the seizure-prone state. In many cases, parallelism of laboratory animal and human manifestations of epilepsy (e.g., genetic, neurophysiologic, and pharmacologic) is striking. Accordingly, laboratory animals with an inborn susceptibility to seizures have been used commonly to study mechanisms of epilepsy and the action of anticonvulsant drugs, including the cannabinoids.

As discussed previously in this section (1.b), some stocks of genetically seizure-susceptible animals (epileptic beagle dog, THC-seizure-susceptible rabbit, and Swiss-Webster mouse) are sensitive to the convulsant effects of  $\Delta^9$ -THC and other THC-like cannabinoids. CBD does not produce convulsions in these stocks. Additionally, CBD has been shown to prevent  $\Delta^9$ -THC-caused convulsions in the THC-seizure-susceptible rabbit,<sup>33</sup> but not in the Swiss-Webster mouse.<sup>48</sup>

An absence or virtual absence of anticonvulsant effects of acute CBD, cannabitol, and  $\Delta^9$ -THC (in nontoxic doses) in the seizure-susceptible Mongolian gerbil,<sup>69</sup> and of acute  $\Delta^9$ -THC in the photosensitive baboon *Papio papio*,<sup>70</sup> has been reported. However, anticonvulsant activity of cannabinoids predominates in other genetically susceptible animals. In the (photosensitive) epileptic chicken, acute  $\Delta^9$ -THC reduced both convulsions and the interictal EEG manifestations of seizures.<sup>71</sup> Acute  $\Delta^9$ -THC has also been shown to block convulsions in the audiogenic seizure (AGS)-susceptible mouse,<sup>25</sup> rat,<sup>25</sup> and rabbit.<sup>72</sup> Further, a wide variety of synthetic analogs of THC have been shown to possess anticonvulsant activity in the AGS-susceptible mouse.<sup>73,75</sup>

In the AGS rat, a relatively specific model for drugs effective in generalized grand mal seizures and partial seizures, CBD exhibited potent and effective anticonvulsant activity.<sup>64</sup> The PI of acute CBD was greater than that of  $\Delta^9$ -THC or cannabitol, and was similar to those of acute PHT, PB, and carbamazepine.<sup>28,64</sup> Further, acute CBD enhanced the anticonvulsant potencies of acute PHT and PB, but reduced the anticonvulsant potencies of acute clonazepam, TMD, and ESM.<sup>64</sup> These findings suggest that CBD might enhance the effectiveness of drugs commonly used for grand mal and partial seizures, but might reduce the effectiveness of drugs commonly used for absence

seizures. Additionally, several synthetic analogs of CBD have been found to be active in AGS-susceptible rats.<sup>28,76</sup> Some salient findings were that the 1, 1 -dimethylheptyl (side-chain) analog of (-)-CBD was 5 times more potent in blocking AGS but also was 15 times more potent in producing (rotorod) neurotoxicity, compared with (-)-CBD.<sup>76</sup> Further, the unnatural (+) isomer of CBD was equipotent in the AGS test and slightly less potent in the rotorod neurotoxicity test than was naturally occurring (-)-CBD.<sup>76</sup> These latter findings are congruent with those MES findings mentioned previously in mice,<sup>63</sup> and together indicate that the anticonvulsant activity of CBD does not depend upon stereospecific binding to a putative, albeit hypothetical, cannabinoid receptor. This would be in contrast to the presumed receptor mechanism of action of  $\Delta^9$ -THC where, for most effects, the natural (-) isomer is active but the unnatural (+) isomer is not.<sup>5,12,46</sup>

### c. Experimentally Produced Focal Seizures

Local epileptogenic activity may be produced by various methods including topical application of convulsant metals (e.g., cobalt, iron, and aluminum) to cortex or repetitive electrical stimulation (kindling) of the limbic structures. The clinical manifestations and response to anticonvulsant drugs depend on the location of the lesion and the type of clinical seizure that results.<sup>60</sup> Generally, the former represents models of simple partial (cortical focal) seizures, and the latter represent models of complex partial (psychomotor) seizures.<sup>60</sup> Both types of models have been used to assess the effects of cannabinoids.

The effects of cannabinoids on cortical focal seizures produced by cobalt, iron, and aluminum have been largely discussed previously in this section (1.c). Acute  $\Delta^9$ -THC precipitated convulsion, and either enhanced (cobalt and aluminum models) or depressed (iron model) focal potentials.<sup>26,51,52</sup> Short-term administration of  $\Delta^9$ -THC in the cobalt model produced both anticonvulsant and convulsant effects, and the former was suggested to involve a reduction in the spread of seizures originating from the cortical foci.<sup>53</sup> In contrast to  $\Delta^9$ -THC, CBD did not evoke convulsions, and did not affect the spontaneously firing foci in cobalt- or iron-induced epileptic rats.<sup>51-53</sup> In the cobalt model, however, acute CBD did abolish the spontaneous clonic convulsions in one study.<sup>52</sup> This anticonvulsant effect was independent of activity on the cobalt foci, and was suggested to involve a depression of seizure generation or spread within the central nervous system.<sup>52</sup> Further, an additional anticonvulsant effect of CBD has been demonstrated in the iron-induced epileptic rat. Acute pretreatment of CBD (but not of PHT) abolished convulsions caused by acute  $\Delta^9$ -THC in these animals.<sup>51</sup>

In models of electrically produced limbic seizures in cats, rats, and baboons,  $\Delta^9$ -THC exhibits antiseizure activity, but its effects are somewhat variable depending upon the experimental preparation and procedures used. In amygdaloid kindled cats, acute  $\Delta^9$ -THC had minimal antiepileptic effects upon established kindled convulsions, but acute and chronic (30 day)  $\Delta^9$ -THC had a significant prophylactic effect on the development of the kindled seizures.<sup>77</sup> This prophylactic effect of  $\Delta^9$ -THC appeared to be due to an increase in seizure threshold at amygdala focus and a reduction in seizure spread to other cerebral structures.<sup>77</sup> In a related study in hippocampal-kindled cats, acute  $\Delta^9$ -THC elevated the threshold for seizures following weak stimulus intensities, but increased the duration of hippocampal afterdischarges following strong stimulus intensities.<sup>26</sup> In amygdaloid-kindled rats, seizures were suppressed by only toxic doses of acute  $\Delta^9$ -THC, and tolerance developed following repeated drug administration.<sup>56</sup> Further,  $\Delta^9$ -THC exerted no prophylactic effect on seizure development in these rats<sup>56</sup> as it did in the amygdaloid-kindled cats.<sup>77</sup> In the photosensitive baboon *Papio papio*, acute  $\Delta^9$ -THC exerted dose-related antiepileptic effects upon established kindled convulsions provoked by electrical stimulation of the amygdala.<sup>70</sup> Electrophysiologic data

suggested that this effect was due to the suppression of propagation of the induced after discharge to distant cerebral structures.<sup>70</sup>

As discussed in part previously in this section (1.c), the comparative effects of acute  $\Delta^9$ -THC, CBD, PHT, and ESM have been studied on kindled limbic seizures in rats.<sup>54,55</sup> All these drugs were generally anticonvulsant but there were marked differences in their electrophysiological effects. At the site (left subiculum) of focal stimulation,  $\Delta^9$ -THC elevated threshold, had no effect on amplitude, and generally increased the duration of afterdischarges.  $\Delta^9$ -THC also increased the afterdischarge durations, bilaterally, in the dorsal hippocampi and cerebral cortices. The increased durations of afterdischarges were purportedly related to an increase in the duration of convulsion caused by  $\Delta^9$ -THC. CBD elevated focal afterdischarge but, in contrast to  $\Delta^9$ -THC, decreased the amplitude and duration of focal afterdischarges, and had no effect on afterdischarge durations at distant brain sites. The electrophysiological effects of PHT were generally similar to those of  $\Delta^9$ -THC on all parameters, and similar to those of CBD only on focal threshold. The electrophysiological effects of ESM were similar only to CBD, and only on the duration and amplitude of focal afterdischarges. Thus in this preparation, the anticonvulsant effects of  $\Delta^9$ -THC, CBD, and PHT appear to be mediated by a reduction in the generation of seizures at the limbic focus. The anticonvulsant effect of ESM appears to involve this same mechanism or a reduction in seizure spread.

The above findings also illustrate the mixed depressant and excitatory properties of  $\Delta^9$ -THC, and the selective depressant properties of CBD. Furthermore, the reference antiepileptic drugs of the above study<sup>54</sup> evoked some signs of central stimulation; i.e., a prolongation of afterdischarges with PHT and a lowering of threshold with ESM. As discussed previously in this section (1.a and 1.c), stimulatory responses (either alone or in combination with depressant responses) are generally associated with  $\Delta^9$ -THC. In contrast, CBD produces relatively selective depressant effects without concomitant stimulation. Some salient examples are the differential effects of  $\Delta^9$ -THC and CBD on the transcallosal cortical evoked response<sup>39</sup> and on spinal monosynaptic reflexes and motoneurons.<sup>42,43</sup> The latter is particularly salient as it provides good evidence that  $\Delta^9$ -THC can enhance and depress synaptic transmission, and that CBD can only depress this phenomenon. Taken together, these findings indicate that CBD is more selective in its actions than  $\Delta^9$ -THC and some standard antiepileptic drugs. This would appear to enhance the potential of this cannabinoid as an antiepileptic drug.

#### *d. Summary*

$\Delta^9$ -THC, CBD, and their analogs have anticonvulsant effects that are relatively selective in terms of the seizure model employed. This selectivity is further influenced by the differential depressant-stimulant properties of  $\Delta^9$ -THC and the relatively specific depressant properties of CBD. CBD exhibits more selective anticonvulsant activity relative to neurotoxicity, and virtually no withdrawal hyperexcitability and convulsant activity as is seen with  $\Delta^9$ -THC.

Acute cannabinoids reliably prevent tonic (maximal), but not clonic (minimal), generalized convulsions caused by electroshock and GABA-inhibiting convulsant drugs like PTZ. Seizures induced by strychnine, a glycine inhibitor, are not blocked by  $\Delta^9$ -THC or CBD and like, PTZ-caused clonic convulsions, may be enhanced by  $\Delta^9$ -THC. Acute cannabinoids also increase the latency to, and the threshold for, clonic convulsions depending on the experimental conditions. With repeated administration, tolerance occurs to the antitonic seizure effects of  $\Delta^9$ -THC and CBD, but reverse tolerance occurs to the elevation of minimal seizure threshold effects of CBD. In these regards, the anticonvulsant profile of CBD is most similar to PHT and presumably reflects a primary mechanism to inhibit the spread of seizures within the central nervous system.

Acute cannabinoids prevent genetically dependent convulsions in epileptic chickens, rats, mice, and rabbits but not in epileptic gerbils or baboons. In epileptic (AGS-susceptible) rats, the anticonvulsant profiles of CBD, PHT, PB, and carbamazepine are most similar, and CBD increases anticonvulsant potencies of PHT and PB but decreases those of clonazepam, TMD, and ESM. Additionally, the unnatural (+) and natural (−) isomers of CBD are equipotent in anticonvulsant and neurotoxic activities which implies a lack of CBD action on a stereospecific cannabinoid receptor.

In cortical focal seizures (produced by topical application of convulsant metals), acute or short-term administration of  $\Delta^9$ -THC generally causes excitatory effects including convulsions. In cobalt epilepsy in rats, short-term administration of  $\Delta^9$ -THC also produces a short-lived reduction of secondarily generalized seizures. In this same preparation short-term administration of CBD was devoid of any activity but, in another study, acute CBD prevented spontaneous convulsion. The latter anticonvulsant effect of CBD (like PHT) was not due to an effect on the cobalt focus. Further, acute CBD is devoid of antiepileptic or excitatory activity in iron-induced epileptic rats.

In models of electrically produced (kindled) limbic seizures in rats, cats, and baboons, acute or repeated administration of  $\Delta^9$ -THC generally exhibits anticonvulsant effects and an elevation of focal seizure threshold (rats and cats) or reduction of seizure spread (baboons). Acute  $\Delta^9$ -THC also increases seizure spread in limbic-kindled rats and subsequently increases the duration of convulsion, once it is initiated. Acute CBD also has anticonvulsant activity in the limbic-kindled rat model and its effects are correlated with a suppression of focal seizure activity. The electrophysiological properties of CBD in this preparation are similar in some regards to both PHT and ESM.

### C. Anticonvulsant Effects of Marijuana and Cannabinoids in Humans

Anecdotal accounts of the anticonvulsant properties of marijuana have circulated for centuries. Various Arabian cultures purportedly employed hashish as a treatment for epilepsy during medieval times.<sup>78</sup> Further, the inhabitants of several countries of southeast Asia commonly use marijuana to treat convulsions, and this practice may have started as early as the 16th century.<sup>2</sup> During the 19th century, O'Shaughnessy, an Irish physician practicing in India, reported that oral marijuana blocked recurrent, tetanic convulsions in a 40-day-old infant.<sup>79</sup> In 1890, Reynolds, a prominent English physician, summarized his 30 years of experience with oral marijuana in the treatment of various maladies, including seizure disorders. He stated that the drug was "very useful for attacks of violent epileptic convulsions, but it was absolutely useless for attacks of petit mal epilepsy."<sup>80</sup>

In more recent years, there have been a few abstracts and short reports dealing with marijuana or specific cannabinoids and epilepsy. In 1949, Davis and Ramsey published an abstract on the antiepileptic effects of the 1, 2-dimethylheptyl analogs of  $\Delta^6$ - $10\alpha$ -THC.<sup>81</sup> The THC analogs were given orally every day, for up to 7 weeks, to five institutionalized children who had grand mal seizures and mental retardation. Two patients became seizure free and the other three patients responded as well as to their previous PB and/or PHT therapy (which had been only marginally effective). In 1967, Keeler and Reifler provided a case report of an adult man with grand mal epilepsy who had three tonic-clonic convulsions during a 3-week interval of his alleged marijuana use (on seven occasions).<sup>82</sup> Prior to this, the man was free of convulsions for 6 months even though he had ceased taking his prescribed PB and PHT. It was pointed out, however, that the reported convulsions did not occur while, or immediately after, the individual smoked the marijuana. In 1974, Perez-Reyes and Wingfield reported that i.v. CBD increased the spike and wave (EEG) activity, relative to i.v. placebo, in an adult epileptic man.<sup>83</sup> The patient was under chloralhydrate-induced light sleep during the sequential placebo and CBD injections. The increase in abnormal EEG activity did

not lead to tonic-clonic convulsions, and the latter were stated to be under control with medication. In 1975, Consroe et al. published a case history of an adult man with grand mal epilepsy who reported additional relief from convulsions during his alleged marijuana use.<sup>84</sup> The patient reported that complete control of seizures occurred only when he continued to smoke marijuana and take his prescribed medication of PB and PHT. In 1976, Feeney reported on the results of a questionnaire survey of alleged marijuana use by epileptic patients.<sup>85</sup> Of 30 epileptics more than 30 years of age, less than 1% reported using marijuana. However, of 42 epileptics under 30 years of age, 29% reported marijuana use, and only 4% of these individuals had discussed their use of marijuana with their physicians. Unfortunately, the effects of marijuana smoking and incidence of seizures were not reported. Finally in 1984, Dow et al. reported that nine cancer chemotherapy patients (out of a total study population of 1565 adults) had a serious reaction to orally administered  $\Delta^9$ -THC.<sup>86</sup> One woman exhibited myoclonic jerking after one (12.5 mg) dose, another woman had the same reaction after five (10 mg) doses, and a third woman had a grand mal seizure after two (10 mg) doses of  $\Delta^9$ -THC. Possible contributing factors in the latter were brain metastasis and a prior history of seizure disorder.

In 1980, Cunha et al. published the results of a controlled study of the effects of CBD in epileptic patients.<sup>8</sup> Fifteen patients (14 to 49 years of age) suffering from inadequately controlled complex partial seizures with secondary generalization were randomly divided into two groups. Patients received, in a double-blind fashion, oral CBD (200 to 300 mg) or placebo daily for up to 4.5 months. Throughout the trial, patients also were maintained on their prescribed medications (single or combined regimens of PB, PHT, ESM, carbamazepine, clonazepam, and primidone). Of the eight patients receiving CBD, four subjects were virtually free of convulsions and three other subjects had partial improvement in their clinical condition. CBD was ineffective in one patient. The clinical conditions of six placebo patients remained unchanged, whereas the condition of one placebo patient clearly improved. In most patients, neither CBD nor placebo significantly changed the interictal EEG abnormalities. Four patients taking CBD and one patient taking placebo complained of somnolence during the trial. No signs of toxicity or serious side effects in any patients were detected on clinical and laboratory examination.

In summary, there are few published reports dealing with the effects of marijuana or specific cannabinoids in human seizure disorders, and almost all are brief accounts of uncontrolled observations or studies in one or only a few patients. Most of the anecdotal reports have ascribed an anticonvulsant effect to marijuana or THC analogs. One report associates increased seizure frequency with a period of intermittent marijuana use, another report attributes a convulsant effect to  $\Delta^9$ -THC, and another credits CBD with exacerbating paroxysmal features on the EEG.

Additionally, there is one placebo-controlled, group-designed trial of CBD in 15 poorly controlled patients with mixed seizures. Virtually all of the patients given CBD improved but virtually none of the patients given placebo improved. The experimental design, patient-sampling procedures, recording of beneficial effects, and duration of treatment appear to be adequate, but concomitant treatments were used, anticonvulsant blood levels were not measured, and drug side effects were not clearly described. Perhaps the most serious criticism of this study is that CBD was administered as an add-on treatment. Although understandable from a clinical point of view, this does not establish that CBD itself is an anticonvulsant. Nevertheless, the addition of CBD to the anticonvulsant regimen did appear to be responsible for the reduction in seizures. This is a potentially important observation since complex partial seizures with secondary generalization are often difficult to treat with currently available drugs.

### III. CANNABINOIDS AND MOVEMENT DISORDERS

#### A. Overview of Movement Disorders

The term "movement disorder" is used for a group of clinical syndromes that have in common a deficit in nonpyramidal motor function and usually one or more of the nonepileptic, abnormal involuntary movements. The parkinsonism syndrome of bent posture, slowness of movement, and tremors of the hands is the best known example, although movement disorders may be found in at least 100 neurological, psychiatric, drug-induced, and other types of medical conditions.<sup>87,88</sup> The following is a brief overview of some aspects of movement disorders which are germane to the present topic, and of definitions as they are used in the text.

Some symptoms that commonly occur in movement disorders include akinesia, bradykinesia, or hypokinesia (slowness in initiating movement or moving body parts); ataxia (incoordinated movement which is not due to paresis, alterations in muscle tone, loss of postural sense, or the intrusion of involuntary movements); catalepsy (in animals, abnormal maintenance of distorted postures; in humans, sudden weakness associated with narcolepsy); chorea (arrhythmic, rapid, brief, and involuntary muscular twitches); choreoathetosis (combination of distal chorea and proximal writhing movements); dyskinesia (a generic term for various forms of spontaneous involuntary movements, often drug induced); dystonia (slow, sometimes sustained involuntary muscle contractions resulting in abnormal position or posture); myoclonus (arrhythmic, abrupt, brief contraction of a single or group of muscles); spasm (involuntary strong, sometimes painful, contraction of a group of muscles of varying duration); and tremor (rhythmic, oscillatory movement, usually due to involuntary alternating contraction of opposing muscles at a joint).<sup>88</sup> The latter may be subdivided into resting tremor (present when limb or body part is relaxed and at rest) and action tremor (present during voluntary muscle contraction; may be most evident when holding a fixed position, throughout the range of a movement or when approaching the goal of the movement). The last may be termed intention, or cerebellar, tremor.

Movement disorders may involve any of the somatic muscles of the body and may be localized (focal), unilateral, or generalized. They may be the result of a wide variety of etiologies, although in many cases the precise causative factors are unknown. Furthermore, most of the latter category, the degenerative (idiopathic) diseases, are chronic and progressive with a multitude of disabling clinical manifestations. The following are some examples. Parkinson's disease (paralysis agitans or primary idiopathic parkinsonism) and some forms of secondary parkinsonism are characterized by resting tremor, muscle rigidity, bradykinesia, and disturbances of posture and gait. Huntington's (hereditary) chorea is characterized by generalized choreic movements of limbs, face, and trunk along with progressive dementia. Some of the more common adult-onset dystonias are spasmodic torticollis (tonic or intermittent spasm of neck muscles causing forced rotation and tilting of the head), writer's cramp (spasm of arm muscles during writing and similar hand movements), and Meige's syndrome (dystonic spasms of facial and jaw muscles). Dystonia musculorum deformans is an often hereditary slowly progressive generalized dystonia with onset before age 20. Tardive dyskinesia due to chronic neuroleptic therapy is characterized by mainly choreic movements of the lower face and tongue, and less prominently of limb muscles. Spasticity (increased muscle tone due to a corticospinal tract lesion) is a common feature of multiple sclerosis, cerebral palsy, and many other conditions. Although in a narrow sense not a movement disorder, spasticity may be associated with abnormal involuntary movements such as tremor and ataxia and add to the impairment of voluntary movement.

Most movement disorders are due to dysfunction of the basal ganglia, along with related centers in the brainstem and/or cerebellum.<sup>87,88</sup> Choreiform movements and

clinical features of Parkinson's disease result primarily from abnormalities of the basal ganglia. Dystonia, tremor, and myoclonus may result from lesions of basal ganglia, cerebellum or brainstem, while ataxia is an important sign of cerebellar disease. In these areas of the brain, abnormalities of neurotransmitter function may play an important part. The cardinal features of Parkinson's disease are thought to result from striatal dopamine deficiency (a consequence of degeneration of the dopaminergic nigrostriatal pathways) and relative cholinergic overactivity.<sup>89</sup> The opposite has been postulated for Huntington's chorea and tardive dyskinesia; namely, dopamine overactivity and relative cholinergic deficiency.<sup>90,91</sup> Overactivity of both dopaminergic and cholinergic systems has been suggested in Meige's disease and some other dystonic syndromes.<sup>92,93</sup> GABA deficiency may be involved in chorea,<sup>91</sup> tardive dyskinesia,<sup>90</sup> and spasticity,<sup>96</sup> and serotonin deficiency in postanoxic myoclonus and perhaps in other neurological disorders.<sup>94</sup>

These abnormalities of neurotransmitter function have provided a rational basis for pharmacotherapy but problems still exist. For example, levodopa (plus carbidopa) is clearly beneficial, and the mainstay of treatment in Parkinson's disease, but not all manifestations (e.g., postural and speech disturbances) nor all patients respond adequately to this therapy, and untoward effects (e.g., choreiform movements) are commonly observed in chronically treated patients.<sup>89</sup> In tardive dyskinesia, and in torticollis and other dystonic syndromes, a great many drugs have been tried, but none has emerged as both predictably beneficial and free of long-term neurologic side effects.<sup>90,92,93</sup> The action tremor of the common, often familial, condition called benign essential tremor may be controlled with diazepam, barbiturates, or propranolol but these drugs fail to ameliorate the cerebellar tremor of multiple sclerosis.<sup>95</sup> Spasticity in some patients with spinal cord injury, cerebral palsy, and multiple sclerosis responds to diazepam, dantrolene, or baclofen but weakness and other troublesome side effects are common.<sup>96</sup>

It is clear that better therapies are needed for many movement disorder patients, especially those with action tremor, spasticity, dystonia, and drug-induced dyskinesia. Early historical observations and anecdotal comments on crude marijuana and recent studies on cannabinoids in patients with multiple sclerosis<sup>6,7</sup> and dystonia<sup>9</sup> have led to speculation about the therapeutic potential of cannabinoids for these movement disorders. In the following sections, neurologic effects of marijuana and cannabinoids that may be relevant to this subject are reviewed.

## B. Neurological Effects of Marijuana and Cannabinoids in Laboratory Animals

Effects of marijuana and cannabinoids have been demonstrated at many levels of investigation in laboratory animals. Perhaps the most evident and striking are gross behavioral effects, concerning which there is an extensive body of literature. The reader is referred to several reviews on the subject.<sup>97-100</sup> In general, marijuana,  $\Delta^9$ -THC and THC analogs produce behavioral signs of both stimulation and depression. In rodents, rabbits, cats, dogs, and monkeys, for example, low to moderate, acute doses may cause hypermotility, hyperreactivity, gait or static ataxia, hypomotility, and catalepsy. Extremely high doses given acutely or chronically may cause these and other signs, including action tremors, muscle spasms, and convulsions. Tolerance develops to many of these effects following repeated administration.

Except at extremely high doses, CBD is devoid of typical THC-like activity.  $\Delta^9$ -THC causes catalepsy in mice, ataxia in dogs, and ataxia, palpebral ptosis, conjunctival injection, crouched posture, and decreased responsiveness in monkeys.<sup>97-100</sup> The latter is one purported behavioral model for THC-like psychoactivity in humans.<sup>101</sup> In view of the potential of CBD as a clinical therapeutic agent, the relative absence of this behavioral syndrome in monkeys after i.v. doses of CBD up to 200 times greater than

those of  $\Delta^9$ -THC is of considerable importance.<sup>102</sup> Nonetheless, in acute studies with very large doses of CBD, behavioral alterations similar to those caused by moderate-dosage  $\Delta^9$ -THC have been reported. In mice, similar behavioral effects (decrease in spontaneous activity, hypersensitivity to external stimuli, ataxia, and abnormal posturing) resulted when i.v. CBD dosages were about 30 times those of i.v.  $\Delta^9$ -THC.<sup>103</sup> In rats, rotorod performance was impaired by both cannabinoids, with i.v. CBD being about 5 times less potent than i.v.  $\Delta^9$ -THC.<sup>28,104</sup> In toxicity studies, CBD and  $\Delta^9$ -THC have been reported to cause qualitatively similar neurologic signs. After acute i.v. administration of lethal or near-lethal doses, tremors, muscle spasms, and occasionally convulsions occurred in both monkeys and rats.<sup>31,32</sup> These CBD-evoked signs occurred at much higher doses and were of shorter duration than those of  $\Delta^9$ -THC.<sup>31,32</sup>

Taken together, these findings indicate that CBD can produce some of the behavioral changes and toxicity that are also produced by  $\Delta^9$ -THC. For these effects, however, CBD is much less potent than  $\Delta^9$ -THC. Moreover, the toxic and lethal doses of  $\Delta^9$ -THC in monkeys and other laboratory animals are more than 100 times greater than those needed to produce behavioral effects in humans.<sup>31,32</sup>

The precise mechanisms of action underlying the diverse behavioral effects of marijuana or cannabinoids are not known. However, a central mode of action is suggested from several lines of evidence. Direct intracranial administration of cannabinoids can produce many of the same behavioral effects that are also seen with peripheral administration of these compounds.<sup>103</sup> Ataxia and catalepsy are two of these effects, and there is some evidence that mechanisms in the cerebellum and basal ganglia, respectively, are involved. Ataxia is a well-known sign of cerebellar deficit, and is one of the most generalizable effects of  $\Delta^9$ -THC. Electrophysiological studies in cats after  $\Delta^9$ -THC have shown altered neuronal activity in the cerebellum associated with slowing of activity in the red nucleus and (hypothetically) with depressed rubrospinal and other descending neuronal influences on the spinal cord.<sup>105</sup> In rats, SP-111 (a water-soluble derivative of  $\Delta^9$ -THC) produced ataxia and a (temporally) correlated decrease in cerebellar neuronal activity.<sup>106</sup> With respect to the latter, SP-111, iontophoretically applied to cerebellar neurons, was shown to potentiate GABA-mediated inhibition.<sup>106</sup> Several electrophysiologic studies, mainly in the anesthetized cat, have linked cerebellar and limbic activity patterns — e.g., electrically-evoked amygdala afterdischarges may be prolonged or suppressed by cerebellar stimulation<sup>107</sup> — raising the question of a relationship at the behavioral level between cannabinoid-induced cerebellar motor and emotional-mental abnormalities.

Catalepsy and hypokinesia are also prominent effects of marijuana and various cannabinoids. Correlative studies implicate multiple mechanisms, including changes in dopamine receptor binding<sup>108</sup> and in acetylcholine turnover<sup>109</sup> in the basal ganglia. In rats catalepsy has been induced by direct injection of  $\Delta^9$ -THC in the caudate-putamen (but not globus pallidus), and parallel pharmacologic data suggested an effect on cholinergic and dopaminergic mechanisms.<sup>110</sup> An indirect interaction with striatal dopamine activity is also suggested by the report that  $\Delta^9$ -THC greatly potentiated the cataleptic effect of reserpine in rats and monkeys.<sup>111</sup> It was also mentioned that levonantradol (a synthetic, nitrogen-containing hexahydrocannabinoid) was more potent, and CBD was less potent, than  $\Delta^9$ -THC in augmenting the cataleptic effect of reserpine in rats.<sup>111</sup> Based on this information, it was suggested that  $\Delta^9$ -THC or other potent cannabinoids might exacerbate hypokinetic symptoms in parkinsonism, and increase the presently marginal effectiveness of reserpine and other drugs used in the treatment of hyperkinetic motor syndromes such as chorea and tardive dyskinesia.<sup>111</sup> These findings and suggestions are interesting and should be confirmed. As will be discussed in subsequent sections, they may have some relevance to the reported effects of marijuana and cannabinoids on spontaneous and abnormal movements in humans.

It is clear from the behavioral and pharmacologic studies cited above that marijuana,  $\Delta^9$ -THC, and other cannabinoids can produce a variety of central effects that may be related to alterations in neuromuscular tone and function as well as other aspects of motor behavior. Neurophysiologic findings provide additional support for this contention. In anesthetized cats<sup>112</sup> and dogs,<sup>113</sup> marijuana,  $\Delta^9$ -THC, and/or related THC analogs depressed a polysynaptic reflex, the linguomandibular reflex. In the cat preparation the THC compounds did not alter a monosynaptic (patellar) reflex. These effects support a supraspinal site of action, e.g., in reticular formation or basal ganglia.<sup>112-114</sup> More recent evidence from studies in unanesthetized spinal cats indicates that cannabinoids also have direct effects on spinal monosynaptic mechanisms. Specifically, low doses of  $\Delta^9$ -THC enhanced synaptic transmission, whereas higher doses of  $\Delta^9$ -THC and all doses of CBD produced depression.<sup>42,43</sup>

In addition, cannabinoids may have direct effects on peripheral nerve conduction and transmission, and on skeletal muscle itself. Impulse conduction in the giant motor axon of the squid was reversibly blocked with external and intraaxonal application of 11-hydroxy- $\Delta^9$ -THC but, surprisingly, not with  $\Delta^9$ -THC.<sup>115</sup> However, a depressant effect on conduction was found for  $\Delta^9$ -THC when it was applied to single myelinated fibers taken from the sciatic nerve of the frog.<sup>116</sup> Further, in the rat phrenic nerve-diaphragm preparation, neuromuscular blockade has been demonstrated following acute *in vivo*<sup>117</sup> and *in vitro*<sup>117,118</sup> administration of  $\Delta^9$ -THC. Data from these studies suggested that  $\Delta^9$ -THC acted on the presynaptic site, although an additional action on the postsynaptic membrane could not be excluded. Also,  $\Delta^9$ -THC-produced neuromuscular blockade has been demonstrated *in vitro* in the isolated sciatic nerve-sartorius muscle preparation of the frog.<sup>119</sup> In this preparation,  $\Delta^9$ -THC blocked neuromuscular transmission by depressing the release of acetylcholine from presynaptic nerve terminals. It was also shown that  $\Delta^9$ -THC depressed the propagation of action potentials in skeletal muscle following supramaximal nerve stimulation, suggesting a depressant effect on ionic conductance mechanisms in the excitable membranes of this tissue.

Effects on skeletal muscle have been reported in mice following 30-day (subcutaneous) administration of low-dose (1 mg/kg)  $\Delta^9$ -THC or CBD.<sup>120</sup> After supramaximal stimulation of the sciatic nerve, a decrease of contractile strength of the gastrocnemius muscle was observed in the cannabinoid-treated animals. This suggests that chronic, as well as acute, administration of cannabinoids can block neuromuscular transmission. Histological analysis of muscle excised from mice treated with either cannabinoid showed myopathic changes (e.g., reduced diameter, necrosis, reduced protein content and increased hydroxyproline content of muscle fibers) which the authors interpreted as muscular dystrophy.<sup>120</sup> The significance of these morphological findings requires clarification since we are not aware of similar reports of cannabinoid-induced myopathy in either laboratory animals or humans. Indeed, in several toxicity studies of  $\Delta^9$ -THC or CBD in rats and monkeys, an absence of specific lesions in skeletal muscle has been reported.<sup>31,32,121,122</sup>

In summary, marijuana,  $\Delta^9$ -THC, and THC analogs produce a wide spectrum of neurological effects in laboratory animals. Behaviorally, these are usually manifested as alterations of motor function: decreased or increased locomotor activity, impaired coordination and balance, decreased muscle tone and reflexes and, at much higher doses, tremors, myoclonic jerks, and convulsions. Paralysis of skeletal muscle is not a prominent feature.  $\Delta^9$ -THC is much more potent than CBD in producing these motor abnormalities. Both central and peripheral sites of action may be involved in the alterations of motor function produced by cannabinoids. These sites include the basal ganglia and other deep cerebral nuclei, cerebellum and its connections, reticular formation, spinal motor neurons, somatic nerves, neuromuscular junction, and possibly

skeletal muscle. Alterations in chemical neurotransmission may be responsible for some of the motor effects. In spite of the large amount of experimental information, a clear picture of how cannabinoids act at the cellular and neurobehavioral levels has not emerged.

### C. Neurological Effects of Marijuana and Cannabinoids in Humans

#### 1. Normal Subjects: Adverse Effects

In the four decades following the classic New York City mayor's study of 1944,<sup>123</sup> a multitude of reports on the physiologic and psychologic effects of crude marijuana and many synthetic cannabinoids, mostly in healthy volunteers, have been published. Major findings of many of these studies have been detailed in some previous reviews.<sup>124-127</sup> Despite differences due to dosage, route of administration, and other study-specific factors, certain findings were relatively consistent. In general, marijuana and most cannabinoids with the fundamental THC structure produced qualitatively similar cardiovascular and autonomic effects (e.g., tachycardia, dry mouth, and conjunctival redness) and psychoactive effects (i.e., the constellation of perceptual and cognitive alterations associated with the subjective "high").<sup>124-127</sup> Potency differences among THC analogs were substantial and were highly dependent on various structural modifications including isomerization of double-bond, side-chain alterations and metabolic hydroxylations.<sup>124,127-129</sup> Non-THC cannabinoids such as CBD,<sup>127,130</sup> cannabichromene,<sup>124</sup> and cannabinal<sup>127,130</sup> were inactive, or virtually inactive, in these regards.

While acute administration of marijuana,  $\Delta^9$ -THC, and related THC homologs has been reported to cause a number of neurological effects in addition to perceptual and cognitive alterations, these have not been found consistently either across or within individual studies, and are more often subjective complaints than objectively demonstrable neurological abnormalities. Nevertheless, ataxia (broadly defined as incoordinated or inaccurate movement), tremulousness, and weakness occur rather frequently and may be considered side effects of cannabinoids with THC-like activity. In humans, such effects have not been reported with CBD<sup>8,131</sup> or cannabinal.<sup>131</sup>

Ataxia resulting from THC activity is approximately proportional to dosage. It has been reliably demonstrated in studies using sensitive equipment to assess hand steadiness, head sway, body sway or stability, and accuracy of pursuit tracking and other complex psychomotor tasks.<sup>123,125,126,132,133</sup> Less-sensitive clinical tests such as the finger-to-nose test, heel-to-toe walking, and assessment of body sway when standing erect without and with eyes closed (Romberg test) may<sup>123,134,135</sup> or may not<sup>136,137</sup> uncover ataxia following marijuana or  $\Delta^9$ -THC administration.

Subjective tremulousness of the body and tremor of the hands have been reported in some, but not all subjects.<sup>123,125,135,136,138</sup> The tremor develops in parallel with ataxia and other symptoms and signs of THC activity. Myoclonic jerks also have been reported in some subjects.<sup>137,139,140</sup> In one study,<sup>137</sup> tremor and myoclonus were documented by electromyography in 8 of 11 volunteers given a large (about 1 mg/kg) oral dose of  $\Delta^9$ -THC or hashish. The abnormal movements involved upper extremities, neck, and leg muscles. They were present at rest and during mild voluntary movement, and disappeared during sleep. The tremors were more like normal shivering than Parkinson tremor; i.e., they were somewhat irregular, two to four (up to six) per second, and associated with variable resting hypertonia. Myoclonus consisted of brief random or occasionally bilaterally symmetric limb or body jerks represented on the electromyograph by 100- to 200-msec phasic potentials of various amplitudes. These were apparently subcortical or spinal in origin since there was no change in the cortical EEG. Patellar reflexes were increased in most subjects but abdominal, plantar, eyeblinking, and pupillary light reflexes, muscle strength and voluntary movements were normal.

Subjective muscle weakness is another common complaint following marijuana or

THC administration.<sup>138</sup> In objective tests, grip strength,<sup>123</sup> muscle strength,<sup>137</sup> and finger- and toe-tapping performance<sup>123,132,136</sup> were normal, although finger strength, as measured by an ergometer, was decreased in one study.<sup>138</sup> A feeling of heavy eyelids<sup>138</sup> and objective ptosis<sup>141</sup> also have been reported. Muscle stretch reflexes may be somewhat increased<sup>134,135,137,141</sup> or unchanged,<sup>126,136</sup> while superficial reflexes are unchanged,<sup>135,137</sup> or decreased<sup>136</sup> in some subjects with acute administration. The Babinski sign (pathologic extension of the large toe with stimulation of the plantar surface of the foot) was absent,<sup>134</sup> suggesting that the function of the voluntary (pyramidal) motor system is normal in spite of these variable other reflex changes.

With repeated, frequent, and adequate dose administration of marijuana or  $\Delta^9$ -THC, tolerance develops to many of their effects. Tolerance develops to the subjective "high", most psychomotor impairments, tremulousness, restlessness, irritability, and tachycardia.<sup>142</sup> Interestingly, a relatively mild and short-lived abstinence syndrome consisting of somewhat similar symptoms — namely, mood changes, restlessness, irritability, hyperactivity, tremulousness, and a fine tremor of the hands — has been seen following abrupt cessation of repeated administration of marijuana or  $\Delta^9$ -THC.<sup>142</sup> Lack of tolerance has been reported for weight gain,<sup>136,142</sup> supine hypotension,<sup>142</sup> conjunctival injection,<sup>142</sup> and fine action tremor of the fingers.<sup>136</sup>

## 2. Neurologic Patients: Therapeutic Effects

During the 19th century, several European-trained physicians used marijuana to treat patients with neurological diseases in their clinical practices. The detailed case reports of O'Shaughnessy indicated that marijuana reduced muscle spasms and produced limb catalepsy in his patients with tetanus or rabies.<sup>79</sup> Shaw claimed that marijuana was effective in tetanus and rabies,<sup>143</sup> and others reported benefit in generalized chorea.<sup>144-148</sup> Reynolds indicated that the drug was "very useful for choreoid and epileptoid clonic spasms but was absolutely useless for tetanus, chorea, paralysis agitans, the tonic spasms of torticollis and writer's cramp, and the jerky movements of spinal sclerosis."<sup>80</sup> These early reports, at least the favorable ones, may well have contributed to the ascendancy of marijuana as an antispasmodic in the U.S. during the late 19th century.<sup>149</sup>

Within the past 10 years, there has been renewed scientific interest in potential therapeutic uses of cannabinoids in epilepsy (Section II.c above) and other neurological disorders. Some of this experimental attention has been focused on patients with disorders of muscle tone. Two survey studies examined the perceived effects of alleged marijuana smoking on spasticity associated with spinal cord injuries. In a 1974 report,<sup>150</sup> five of eight patients indicated on interview that they experienced decreased skeletal muscle spasticity during their marijuana intoxications. In a 1982 report,<sup>151</sup> data were compiled from questionnaires mailed to spinal-cord-injured persons. Of 24 persons (56% of all survey responders) who reported marijuana usage during the course of their symptoms, 21 (88%) indicated a reduction in spasticity, and 3 (12%) no change. In an additional case report,<sup>152</sup> a patient suffering from multiple injuries and another from multiple sclerosis alleged that marijuana smoking relieved their pain and skeletal muscle spasms. These cases add little to information published 100 to 150 years ago.<sup>3,79,80,143,149</sup>

Two reports have been published concerning the effects of orally administered  $\Delta^9$ -THC in multiple sclerosis patients. In 1981, Petro and Ellenberger<sup>6</sup> reported on nine patients given  $\Delta^9$ -THC (5 or 10 mg) or placebo, under a double-blind, cross-over design. Compared with placebo, 10 mg of  $\Delta^9$ -THC significantly reduced spasticity as quantified by clinical and electromyograph measurements. Reported side effects of both doses were negligible in these patients (who were naive to prior marijuana usage).

The authors also reported that  $\Delta^9$ -THC produced clinical benefit in three additional patients with tonic spasms but not in other patients with cerebellar disease.

In 1983, Clifford<sup>7</sup> reported on the effects of  $\Delta^9$ -THC, 5 to 15 mg, in eight multiple sclerosis patients presenting with disabling tremors and ataxia. Of these eight patients, five reported subjective improvement of tremor and sense of well being, but this was without objective clinical verification. Two patients had both subjective and objective improvement. The latter was demonstrated by polygraph recording of head movement and by handwriting analysis, but not by finger-to-nose testing. These objective responses were then challenged with a placebo under single-blinded conditions, and tremor and writing performance worsened. Also, all eight patients (four with and four without prior experience with marijuana) experienced a subjective "high" with the 15-mg dose of  $\Delta^9$ -THC, and two patients reported dysphoric sensations with lower doses.

Recently at our institution, an open-label, dose-rising study has begun to evaluate the therapeutic efficacy of CBD in patients with dystonia.<sup>9</sup> This study was motivated by anecdotal reports of improvement of this difficult-to-treat condition with marijuana smoking.<sup>153,154</sup> Patients with focal or generalized dystonia on stable doses of other medications are being selected. CBD, obtained from the National Institute on Drug Abuse, is dissolved in sesame oil and placed into clear gelatin capsules. CBD is started at 100 mg/day, given in two doses. The daily dosage is increased by 100 mg/day at 1-week intervals until an optimal response is seen or 600 mg/day is given. Patients' disabilities are assessed by one of the authors (S. R. S.) at weekly intervals according to standardized rating scales for the dystonias.<sup>155</sup>

Thus far, two patients with cranial dystonia and two patients with generalized dystonia have completed the trial. The first patient had a 9-year history of frequent and severe dystonic spasms of eyes, face, and neck (Meige's syndrome) despite maximum tolerated doses of trihexylphenidyl (5 mg/day), clonazepam (2.5 mg/day), and baclofen (130 mg/day). His mean dystonia score and spasm frequency gradually decreased during CBD administration and maximal improvement, about 40%, occurred with CBD doses of 300 to 500 mg/day. Side effects were mild dry mouth and occasional lightheadedness. Withdrawal of CBD or administration of placebo (under single-blinded conditions) resulted in an increase in the patient's disabilities. The second patient had torticollis of 2 years' duration. She also had bilateral action tremor of the hands and hypertension, the latter being treated with atenolol, 50 mg/day. CBD administration resulted in a dose-related improvement in all three symptoms. Maximal improvement of the torticollis was about 35% at CBD doses of 400 to 600 mg/day. As in the first case, CBD benefit was confirmed by an increase in the torticollis following CBD withdrawal. Side effects were dry mouth and slight psychomotor slowing.

A third patient with generalized torsion dystonia (*dystonia musculorum deformans*) of 20 years' duration, had obtained moderate benefit from high-dosage trihexylphenidyl. As CBD was added, his dystonic spasms (especially of his more severely affected right leg) lessened, and mild intention tremor of the right upper extremity disappeared. Overall improvement due to CBD was about 35%, but was sufficient to permit independent ambulation for short distances (e.g., between house and car). Side effects of CBD were mild sedation and occasional lightheadedness. The fourth patient, a man in his 40s with an 8-year history of parkinsonism, had developed disabling generalized action dystonia as a peak-dose side effect of Sinemet (levodopa plus carbidopa) administration. At the lowest CBD dose (100 mg/day), the patient noticed a reduction of the dystonia. At 200 mg/day, the dystonic component of the dyskinesia was objectively improved without change in the parkinsonism, leaving a moderate and less disabling generalized choreoathetosis at rest as the main movement side effect of the Sinemet. At 400 mg/day, there was a noticeable (about 35%) worsening of the parkinsonism signs and mildly symptomatic orthostatic hypotension. Following withdrawal of the

CBD, there was a 4-day period of marked exacerbation of the dystonia and several weeks of a decreased requirement (from 1100 to 900 mg/day levodopa) for Sinemet. The above results indicate that CBD may produce improvement in symptoms of dystonia. Additional patients will be included to attempt to confirm these encouraging, but preliminary, results.

### 3. Summary

Marijuana,  $\Delta^9$ -THC and closely related homologs can alter neuromuscular function in both health and disease. In normal individuals, signs and symptoms suggesting cerebellar dysfunction — ataxia, tremulousness, and subjective weakness — have been reported most frequently. These effects on normal subjects are variable in their occurrence, and are weak in relation to the more obvious psychoactive, cardiovascular, and autonomic effects. In patients with neurologic disorders affecting muscle tone and movement, anecdotal reports have indicated that marijuana may have beneficial effects. One controlled study showed that acute  $\Delta^9$ -THC had antispasmodic effects in a group of multiple sclerosis patients. Another (uncontrolled) trial of acute  $\Delta^9$ -THC in multiple sclerosis patients showed that the cannabinoid reduced action tremor and ataxia in a few, but not all, cases. Finally, preliminary data from our uncontrolled trial of repeated (6 weeks) administration of CBD in dystonia suggest that this cannabinoid may improve symptoms of both tonic (dystonic posture and pain) and phasic (dystonic spasms and tremor) components of the disorder. Reported side effects of CBD were mild and did not include the typical disturbing changes in autonomic function, mood, and mentation associated with  $\Delta^9$ -THC.

## IV. SUMMARY AND CONCLUSIONS

One promising therapeutic area for CBD and possibly some of its analogs is epilepsy. Clinical data and substantial preclinical data show that CBD has a relatively novel pharmacological profile. Unlike  $\Delta^9$ -THC, acute CBD is devoid of psychoactive, cardiac, and other major untoward effects in normal humans. In laboratory animals, CBD exhibits more selective anticonvulsant activity relative to neurotoxicity than does  $\Delta^9$ -THC. In this regard, CBD is similar to several antiepileptic drugs such as phenytoin (PHT), phenobarbital, and carbamazepine. Development of tolerance is not a prominent feature of CBD or PHT as it is for  $\Delta^9$ -THC. CBD does not cause central stimulation or convulsant effects in seizure models like  $\Delta^9$ -THC. In kindled limbic epilepsy, CBD has more complete antiseizure effects at the limbic focus and no excitatory effects on seizure generation or spread compared with  $\Delta^9$ -THC and the antiepileptic drugs PHT and ethosuximide. Further, CBD has selective depressant effects on neurotransmission in cortex and spinal cord which in conjunction with its differential anticonvulsant effects in animal seizure models, may relate to an inhibition of seizure spread as an additional mechanism of action.

Laboratory animal findings suggest that CBD would be beneficial for partial seizures and generalized grand mal seizures. This has been tentatively verified by the results of the only published study of CBD in epileptic patients. Preclinical data suggest that CBD would not be effective in absence seizures, and may reduce the anticonvulsant effects of the drugs commonly used to treat these disorders. Further, use of marijuana,  $\Delta^9$ -THC, and other THC analogs should be discouraged in patients with any seizure disorder until more clinical information is available.

Treatment of movement disorders is another promising area for cannabinoid therapy. Improvement in abnormal movements and muscle tone may be mediated by effects at more than one site; i.e., basal ganglia, cerebellum, reticular formation, spinal motor neurons, somatic nerves, neuromuscular junction, and skeletal muscle. While

$\Delta^9$ -THC evokes both stimulant and depressant effects and CBD causes only selective depression of activity at many of these sites, the precise mechanisms of action of either cannabinoid are still unknown.

Marijuana by mouth or inhalation has been used for muscle spasms of various etiologies for many years. In a controlled study of multiple sclerosis patients with spasticity,  $\Delta^9$ -THC was of some benefit. However, both marijuana and  $\Delta^9$ -THC may have undesirable side effects at the dosages necessary to reduce muscle tone. In contrast, CBD, in combination with optimal standard therapy, has improved motor symptoms in four patients with dystonia without a significant increase in adverse effects. If confirmed, these findings would be of special significance since current drug treatment of dystonia is only partially effective and is usually accompanied by dose-limiting side effects. Additionally, CBD may have therapeutic potential for other hyperkinetic movement disorders such as drug-induced dystonia and perhaps tardive dyskinesia and generalized choreoathetosis, but both CBD and  $\Delta^9$ -THC may increase the hypokinesia of parkinsonism.

Additional clinical trials of CBD in patients with epilepsy and movement disorders are warranted to confirm predictions from the laboratory and preliminary findings from the clinic. Animal studies are needed to determine chronic effects and interactions of CBD and standard drugs commonly used for these disorders. Studies in animals aimed at uncovering the loci and mechanisms of action of CBD and at defining the structure-activity relationships of CBD analogs have been productive, and should be continued. In normal human subjects, there is great need for basic pharmacokinetic and pharmacodynamic data of CBD, including determinations of oral bioavailability, plasma protein binding, rate of elimination, and other related parameters. Assessment of the full potential of cannabinoids for neurological disorders can only be made with these additional data obtained from laboratory animals and human subjects and patients.

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