Most patients have had the classic bursts of small-amplitude, high-frequency rotary oscillations causing oscillopsia, defined as intermittent uniocular microtremor [8]. Others, however, have had a slower, larger-amplitude intorsional movement causing vertical and torsional diplopia. We have termed this movement *macrorotary deviation* (MRD). MRD has occurred most often in association with the more classic IUM [6–8, 10, 11], but in a few patients it has been the only or predominant eye movement abnormality [2, 9, 12]. Other associated motility problems have included intermittent overaction of the ipsilateral superior oblique muscle [10–12], ipsilateral superior oblique paresis [7, 10], and, in our patient, an intermittent Brown's syndrome.

We suspect that all of the grossly visible movements (MRD, intermittent overaction of the superior oblique, and intermittent superior oblique tendon sheath syndrome) represent the same rotary entasia expressed differently when assessed by varying techniques. An alternate-cover test would reveal an overaction of the superior oblique muscle; an apparent Brown's syndrome would be diagnosed if the motor anomaly occurred during attempted gaze inward and upward; and the MRD itself would be observed only during direct observation.

The cause of IUM and MRD is unclear. Their frequent concurrence implies a continuum of motor anomalies. Electromyographs of the two types of movements are similar, with evidence of chronic denervation, supporting the idea that both are manifestations of superior oblique myokymia [7, 9]. Kommerell's patient with MRD had a more stable rate of firing than others with IUM, suggesting that the firing pattern of the abnormal motor units may determine the clinical picture [9]. All electromyographic evidence to date supports Hoyt's original suggestion that SOM is primarily a nuclear disorder [7–9].

Possibly pertinent to SOM is a report by Baker and Bertoz, who evaluated oblique nystagmus induced by vestibular lesions in alert "encephale isolé" cats [1]. Using intra- and extracellular recordings from inferior and superior oblique motor neurons, they noted a "rhythmic oscillation" in the electrical discharge from the oblique motor neurons immediately after a sudden decrease in the stimulation rate. The occurrence of such a "rhythmic oscillation" immediately after a sudden decrease in the stimulation rate could be the physiological basis for the clinical observation that the uniocular microtremor is most easily provoked by moving the eye into and then out of the field of action of the superior oblique muscle.

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Tetrahydrocannabinol for Tremor in Multiple Sclerosis

David B. Clifford, MD

Based on one patient's enthusiastic report, eight patients with multiple sclerosis, seriously disabled with tremor and ataxia, were given oral tetrahydrocannabinol. Two demonstrated improved motor coordination.

Clifford DB: Tetrahydrocannabinol for tremor in multiple sclerosis. Ann Neurol 13:669–671, 1983

A young man with multiple sclerosis (MS) and a postural tremor maximal in the head and neck discovered that his tremor was diminished by smoking marijuana. This study was undertaken to see if a similar response

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could be obtained using oral tetrahydrocannabinol (THC).

Methods

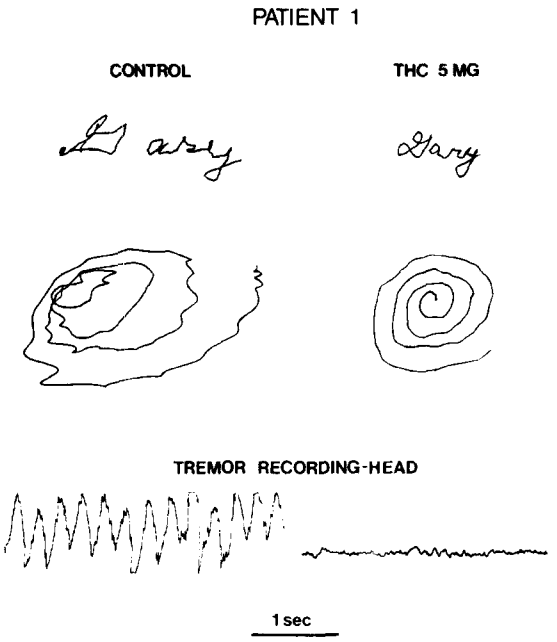
Eight patients (four men and four women) with MS, disabling tremors, and ataxia were selected. All patients had a diagnosis of definite MS by the criteria of Rose and colleagues [7]. Patients ranged in age from 21 to 49 years (mean age, 32.7 years). The protocol, approved by the Washington University Human Studies Committee and the US Food and Drug Administration, included obtaining informed consent and then screening the electrocardiogram and blood chemistries to assure that there was no active cardiac, renal, or hepatic dysfunction. A baseline video recording was made for each patient showing the movement disorder at rest, speech, finger-nose-finger test, heel-knee-shin test, gait when possible, and when picking up a coin with either hand, using a spoon, using a pencil, handwriting a sample of his or her name, and drawing a spiral. A brief mental status examination tested recall of three objects, number sequence repetition, and subjective estimate of psychological effects, including sedation, "high," discomfort, faintness, and tremor, as judged by the patient and by the author. A test dose of THC was then given, and the test battery was repeated at two and four hours following the dose. The initial dose of 5 mg was increased by increments of 5 mg until unpleasant side-effects were encountered or an apparent therapeutic response occurred. Minimum time between doses was six hours. Objective response was challenged with a single-blinded placebo of identical appearance. The THC and placebo were supplied by the National Institute on Drug Abuse. Tremor recording on Patient 1 was obtained by recording movement artifact from gold disk electroencephalographic leads applied to either side of the face with a Grass Model 6 EEG at a gain of 2 μV/mm.

Results

Patients were severely disabled, with a mean Kurtzke disability score [4] of 6.88 (range, 5 to 9). Half had used marijuana in the past; two of the eight were regular users. All patients experienced a subjective "high" with the largest dose used; two experienced a dysphoric sensation. Doses ranged from 5 to 15 mg of THC. Five of eight patients had mild subjective improvement in tremor and sense of well-being without objective improvement. Two patients had both subjective and objective improvement. These will be described in somewhat greater detail.

Patient 1

A 30-year-old man had a ten-year history of MS consisting of exacerbations and remissions, resulting in paraparesis, diplopia, ataxia, numbness and paresthesia in all extremities, urinary retention, incontinence, and impotence. Medical treatments had included adrenocorticotropic hormone, corticosteroids, and azathioprine. A disabling tremor had been a consistent problem for more than a year. Tremor was maximal in the head and neck and resulted in particular problems eating, because it increased as efforts were made to put food in the mouth. The tremor was diminished but not abolished when the patient was supine with his head fully supported. It disappeared with sleep. Treatment with diazepam, alcohol, propranolol, and physostigmine were uniformly unsuccessful. Marijuana had been used to control the tremor on an almost daily basis for at least one year prior to this study without evidence of diminishing response. The initial 5 mg dose of THC resulted in a decrease in head and neck tremor within thirty to sixty minutes which lasted approximately six hours. The dose resulted in a very mild "high" which did not appear to impair judgment. Mild hand ataxia seen in finger-nose-finger testing was little changed, but the patient's ability to write was considerably improved (see the Figure) and his use of eating utensils was markedly improved. When placebo capsules were substituted, no improvement occurred in spite of a "high" sensation. Repeated testing with active drug on two occasions again demonstrated the response.



Handwriting sample and movement artifact from head, recorded before and 90 minutes after ingestion of 5 mg of tetrahydrocannabinol.

Patient 2

A 30-year-old female had a fourteen-year history of MS consisting of a relapsing and remitting cord syndrome, dysarthria, bowel and bladder disturbances, persistent diplopia with ophthalmoplegias, head titubation, and hand ataxia such that she had been unable to feed herself or write for four years. There was no response to doses of 5 and 10 mg of THC, but several hours after administration of 15 mg, she could control her hand sufficiently to make a legible copy of her name, whereas she had difficulty making an *x* prior to treatment. Administration of placebo resulted in illegible writing, whereas a second dose of 15 mg of THC again increased hand control for more than six hours. Other areas of motor functioning remained as impaired as before treatment.

Discussion

The therapeutic potentials for cannabinoids [6] include treatment of nausea, glaucoma, asthma, epilepsy, spasticity [5], and now tremors. Tetrahydrocannabinol, the major active ingredient of marijuana, has prominent psychoactive properties that make it too toxic to justify its use where there are more specific therapies. Once a potential action of a class of drugs has been identified, however, natural and synthetic analogs may be tested to establish the useful drug characteristics and reduce the nonspecific actions.

Knowledge of the mechanisms of the various actions of the cannabinoids is at present in a seminal state, though there are many plausible cellular or neurotransmitter effects that would explain their therapeutic and toxic actions. Among neurotransmitters, the cholinergic effects characterized by Domino [2] are well studied. Effects on the gamma-aminobutyric acid, serotonergic, and beta-adrenergic systems [1, 3] may also be germane to the effects on tremor.

Discussion of the mechanism of action of the drug in this instance is especially difficult given the paucity of knowledge about the mechanisms of tremor in general [8] and particularly of the complex tremor seen in the responders in this series. It seems reasonable to remain receptive to the possibility that either intention or essential tremor may be affected by THC. The ataxia often seen in MS is not highly responsive; most of the patients had no objective response. These were very advanced cases, however; some therapeutic response may have been masked by the severity of the lesions.

The importance of this observation of a specific tremor-blocking effect of THC lies in the implication of a new therapeutic action for cannabinoids. As less toxic derivatives in this series of drugs are developed, they should be evaluated for effects on tremors and ataxia.

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Lithium Interferes with Reserpine-Induced Dopamine Depletion

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Long-term lithium treatment attenuated the hypokinetic effect of reserpine in a patient with tardive dyskinesia. In rats, prophylactic lithium administration inhibits reserpine-induced dopamine depletion in the brain. These data indicate that lithium may limit the therapeutic efficacy of reserpine in tardive dyskinesia.

Reches A, Hassan MN, Jackson V, Fahn S: Lithium interferes with reserpine-induced dopamine depletion. Ann Neurol 13:671–673, 1983

Tardive dyskinesia and tardive dystonia are extrapyramidal movement disorders induced by chronic treatment with neuroleptic drugs [2, 4]. Tardive dyskinesia is currently treated with the dopamine (DA)-depleting agents reserpine and tetrabenazine [11, 12]. Because tetrabenazine has recently been shown to block DA receptors [16, 18, 19], reserpine is presently the drug of choice. In certain psychiatric conditions, including schizoaffective disorders and mania, neuroleptic drugs and lithium are given concurrently [14, 17]. Patients with this combination of drugs occasionally develop tardive dyskinesia or tardive dystonia, creating the specific problem of treating the extrapyramidal disorder during continuous lithium administration.

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