EXHIBIT E

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ANTICONVULSANT NATURE OF MARIHUANA SMOKING

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Marihuana smoking, in conjunction with therapeutic doses of pheno-barbital and diphenylhydantoin, was apparently necessary for controlling seizures in one 24-year-old epileptic patient.

ANECDOTAL accounts of beneficial therapeutic effects of Cannabis sativa have been known throughout recorded history. (1) The classic description by O'Shaughnessy (2) in 1842 of the ameliorative effects of marihuana extract on "infantile convulsions," "hydrophobia," and "lockjaw" invite speculation as to the anticonvulsant effect of the drug. Other 19th century physicians reported that marihuana preparations were of benefit in controlling various spastic and seizure states, (3,4) although entirely useless in states of "true chronic epilepsy" such as petit mal. (4) Synthetic derivatives of delta-9-tetrahydrocannabinol, the main psychoactive ingredient of marihuana, have been reported to be of val;ue in the treatment of human epilepsy, although explicit details are absent in the abstract-report. (3) Finally, there is also a published report in which grand mal convulsions in a 20-year-old man were exacerbated by smoking marihuana. (4)

These references are essentially the only available literature on the relationship between marihuana and human convulsions, which obviously indicates a paucity as well as a contradiction of information. The following case report describes the possible beneficial effect of marihuana in human epilepsy.

Report of a Case

A 24-year-old man has been seen in a neurology outpatient clinic for a period of eight years for control of his epileptic seizures. His history included febrile convulsions at 3 years of age and epileptic seizures since the age of 16. Since that age, the patient has been taking diphenylhydantoin sodium, 100 mg four times a day, and phenobarbital, 30 mg four times a day. Control seizures with this regimen was incomplete, and the patient complained of attacks about once every two months. From the age of 16 to 22, the incidence of seizures increased to one attack per month to one per week.

At 22 years of age, the patient began smoking marihuana (two to five joints per night) while continuing the prescribed anticonvulsant drug therapy. During this period, attack did not occur as long as the patient continued to take the combination of all three drugs. The patient's condition could not be maintained on marihuana alone, because on two occasions he experienced an attack three to four days after running out of his prescribed medication.

Neurological work-up has recently been done on the patient and he has been thoroughtly interviewed, because of the possible association between marihuana and epileptsy. The patient was found to have abnormal paroxysmal bursts of spike and slow-wave electroencephalographic discharges bilaterally, and his condition was diagnosed as grand mal epilepsy. The patient showed no other physical or emotional disability and did not admit to smoking cigarettes, drinking alcohol, or taking any other drugs. Plasma level of diphenylhydantoin was 7.4 mcg / ml; ohenobarbital level was 11 mcg /ml; and folic acid, 4.5mcg / ml.

The patient apparently complies with his dosage regimen, since he has a history of regular clinic visits and refilled drug prescriptions.

Comment

This case suggests that marihuana may possess an anticonvulsant

effect in human epilepsy. Previous reports have alluded to this possibility. (1-3,5) Moreover, the antiseizure properties of delta-9-tetrahydrocannabinol have been demonstrated in a wide variety of experimental animal species. (7-9) It has been shown in laboratory-animal seizure models that the tetrahydrocannabinols show a differential activity against major seizures without altering the sequelaw of minor seizures. (7) Thus, the present case appears to bear out the prediction from the animal studies while at the same time possibly explaining marihuana's observed lack of effect in petit mal epilepsy. (4)

Theoretical calculations can be made to elucidate the probable blood level range for delta-9-tetrahydrocannabinol. A sample of the patient's marijuana was analyzed for tetrahydrocannabinol content by gas chromatography, and was found to contain 1.2% by weight total cannabinoids. One twelfth of the total cannabinoids, or 0.1% by weight, was accounted for by delta-9-tetrahydrocannabinol. Assuming 1 gm of marihuana per joint and correcting for pyrolysis (50%) and lung-absorption losses (20%), the inhalation dose of delta-9-tetrahydrocannabinol to the patient (weight, about 65 kg [143]) would be 6.15 mcg / kg. It is known that doses of 5 mcg to 7 mcg / kg of delta-9-tetrahydrocannabinol produce psychological and physiological effects in steady marihuana smokers. (10) Moreover, after an intravenous bolus of delta-9-tetrahydrocannabinol, marihuana smokers show lower blood levels and shorter half-lives (28 hours) for the drug than nonusers (half-life, 57 hours). (10) Since the half-life is 28 hours in steady smokers and this patient used two to five joints per evening, little of the drug would be eliminated and the blood levels would be expected to climb rapidly during the evening.

The subtherapeutic blood level of diphenylhydantoin in this patient, 7.4 mcg / ml (normal range, 10 to 25) was not unexpected, since phenobarbital is know to induce the formation of enzymes that metabolize diphenylhydantoin. Even when the blood levels of diphenylhydantoin are less than the normal range, the combination of the two drugs is known to be clinically effective. (11) The blood level of 11 mcg / ml of phenobarbital found in this patient is within the normal therapeutic range (10 to 20).

In summary, marihuana smoking in conjunction with routine doses of phenobarbital and diphenylhydantoin was apparently necessary for controlling seizures in one 24-year-old patient. However, the present case is in direct contrast to the single previously reported case of marihuana smoking exacerbating seizures in one patient with grand mal epilepsy. (6) The possibility that delta-9-tetrahydrocannabinol or other cannabinoids may be useful or detrimental in major seizures needs further investigation.

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