catnip had a biphasic effect. At levels up to 1800 mg/kg, increasing dose levels caused an increase in the number of chicks that displayed 2 sequential 1-min sleep periods during the first 20 min of observation. Higher dose levels (i.e. 2000 and 2200 mg/kg) showed a decrease in the number of chicks that were affected in this way. There was no increase in mortality at any dose level, so the lethal dose 50% must be higher than 2200 mg/kg.

Discussion. Since catnip is widely used in herbal medicine and a potential drug of abuse, it is important to gain greater insight into its mechanism and site of action. It is clear that the alcohol extract of catnip causes biphasic effects in young chicks. Low and moderate dose levels cause an increase in the number of animals that sleep, while high levels cause a decrease in this number. It will be important to isolate that active agent (or agents), identify it, and elucidate its pharmacology. In an attempt to achieve this goal, we are currently screening other solvent extracts of catnip for pharmacological activity and determining how the ethanol extract of catnip interacts with other psychopharmacological agents.

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Anticonvulsant activity of farnesylacetone epoxide – a novel marine natural product

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Summary. A marine natural product, farnesylacetone epoxide, which is chemically related to juvenile hormone, has anticonvulsant properties at nonsedative doses in mice.

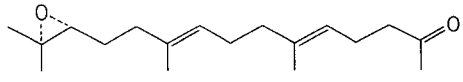
A dichlormethane extract of a brown alga, *Cystophora moniliformis,* was found to have anticonvulsant activity in mice. The active constituent farnesylacetone epoxide (**I**) (figure 1) was isolated and found to be an analogue of juvenile hormone[1]. The pharmacological activity of farnesylacetone epoxide has been studied and the anticonvulsant properties compared with phenytoin.

Farnesylacetone epoxide could protect mice against all phases of the convulsive response to electroshock but only after an i.p. dose of 600 mg/kg (table). Phenytoin at this dose level could not prevent the clonic convulsive response after electroshock, although doses as low as 30 mg/kg i.p. did prevent the tonic limb flexion and tonic extensor phases.

The effect of farnesylacetone epoxide and phenytoin on convulsions induced by electroshock (30 mA, 160 V, 0.2 sec via corneal electrodes) or metrazol (110 mg/kg i.p.) in mice

	Farnesylacetone epoxide	Phenytoin
Protection against electroshock (ED_{50} mg/kg i.p.)		
Tonic limb flexion	550	20
Tonic extensor	370	20
Clonic convulsion	460	> 300
Protection against metrazol (ED_{50} mg/kg i.p.)		
Tonic limb flexion	320	25
Tonic extensor	190	20
Clonic convulsion	> 600	> 300
LD_{50} (mg/kg i.p.)	> 900	190

Fig. 1.



Farnesylacetone epoxide at 300 mg/kg i.p. did prevent the tonic extensor phase of metrazol (110 mg/kg i.p.) induced convulsions. However a dose of 600 mg/kg i.p. was necessary for full protection of tonic limb flexion, tonic extensor and the lethal consequence of the convulsion induced by metrazol. Both farnesylacetone epoxide and phenytoin could not prevent the clonic convulsive response to metrazol at any dose level. As with electroshock, phenytoin did prevent the tonic limb flexion and tonic extensor phases of the metrazol response at doses as low as 30 mg/kg i.p. After oral administration farnesylacetone epoxide was inactive against all phases of electroshock or metrazol induced convulsions.

For electromyographic studies mice were anaesthetized with pentobarbitone (80 mg/kg i.p.) and recording electrodes (fine stainless steel pins) were implanted in the interdigital muscles of the ipsilateral foot and in the anterior tibialis muscle of the contralateral hind limb. Stimulating electrodes were placed close to the sciatic nerve.

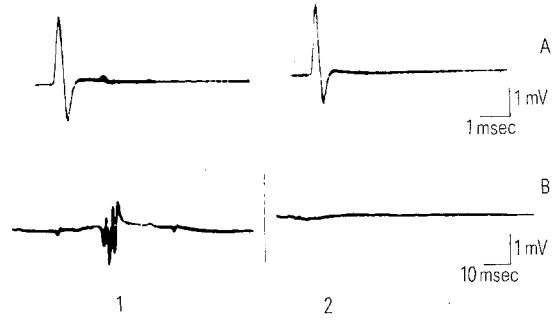


Fig. 2. The effect of farnesylacetone epoxide on peripheral neuromuscular transmission (A) and polysynaptic reflex discharge (B) in an anaesthetized mouse. 1. Control responses; 2. responses 15 min after the injection of farnesylacetone epoxide (300 mg/kg i.p.).

Stimuli delivered to these electrodes evoked a compound muscle action potential in the ipsilateral limb which was used to monitor effects on peripheral neuromuscular transmission. Small discharges were also evoked in the contralateral limb which monitored transmission across polysynaptic pathways in the spinal cord. Effects were monitored for 1 h or longer depending on activity. Farnesylacetone epoxide at 300 mg/kg i.p. completely blocked the discharge in the contralateral limb but had no effect on the compound action potential in the ipsilateral limb (figure 2). This effect of farnesylacetone epoxide was observable 10 min after i.p. injection and was still evident 1 h later. Phenytoin at 400 mg/kg i.p. had a similar effect in blocking polysynaptic reflexes without any effect on peripheral neuromuscular transmission.

These results suggest that high doses of farnesylacetone epoxide and phenytoin do not effect transmission at the peripheral neuromuscular junction but do block polysynaptic transmission in the spinal cord.

Farnesylacetone epoxide initially caused hyperactivity at doses higher than 300 mg/kg i.p. followed by ataxia and finally a loss of the righting reflex in mice. These and other effects, such as hypothermia and ataxia, appeared within 5 min after injection and lasted longer than 1 h but usually were absent 2 h after injection. In contrast, the observable effects of phenytoin in mice, although similar, were longer in onset and duration. Phenytoin was more toxic than farnesylacetone epoxide after i.p. administration. Farnesylacetone epoxide at doses greater than 300 mg/kg i.p. but not p.o. did potentiate barbiturate sedation and also prevented the tremor and cholinergic symptoms after oxotremorine in mice.

A 50% inhibition of rat liver mitochondrial respiration in vitro was caused by farnesylacetone epoxide at a concentration of 5 μM as compared to the standard, rotenone, which caused a 50% inhibition at 0.5 μM. Farnesylacetone epoxide also caused a nonspecific block to agonists on the isolated guinea-pig ileum. Thus an organ bath concentration of 1×10^{-4} M reduced the contractile response to acetylcholine, nicotine and histamine by 50%. This concentration also inhibited the spontaneous beating of the isolated guinea-pig atria.

The pharmacological activity of farnesylacetone epoxide is in many ways similar to the polyhalogenated monoterpenes isolated from red alga[2]. The anticonvulsant activity is observed after high parenteral doses and not observed after oral administration. There is a nonspecific block of the response of isolated organs such as the ileum and atria to agonists. Mitochondrial respiration is inhibited which may relate to the sedative and anticonvulsant properties.

The pharmacological properties of farnesylacetone epoxide are not grossly altered in structural analogues which may suggest a nonspecific mode of action, however, the lack of knowledge of the precise mechanism of action of known anti-convulsants makes comparative evaluation of the mechanism of farnesylacetone epoxide very difficult.

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A comparative study of the effects of muscimol and diazepam on the recall of noxious events[1]

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Summary. Muscimol induced in rats a recall deficit which possibly results from a dissociation of learning. In one out of the 2 experimental conditions studied, a cross dissociation of learning was found between diazepam and muscimol.

Several lines of research suggest a GABA involvement in memory processes. Blockade of GABA transaminase with amino-oxyacetic acid (AOAA) leads to a lack of consolidation across sessions[2]. Benzodiazepines, drugs acknowledged to facilitate GABA transmission[3], have been found - perhaps through a retrieval impairment - to exhibit amnesic-like effects[4].

In order to test further the hypothesis of a GABA control on memory, the effects of a direct GABA agonist, muscimol[5], were investigated in 2 experimental situations in which benzodiazepines were found to exert amnesic-like activity. Furthermore, an attempt was made to examine the relationship between the GABA agonist activity of benzodiazepines and their amnesic-like activity.

Material and methods. The experiments were carried out on male Wistar A.F. rats (180–220 g) housed 8 per cage with free access to food and water unless otherwise noted, and maintained in a 12 h/12 h light-dark cycle.

Situation A. The situation used has been described previously[6]. Briefly, the test situation was a ($36 \times 36 \times 30$ cm) translucent box with, in a corner, a drinking bottle the drinking tube of which terminated at a height of 3 cm above an electrifiable grid floor. The rats were deprived of water (but not of food) during the 16 h preceding their introduction into the test box.

Situation B. The test-apparatus were 3 operant chambers (housed in ventilated sound insulating cubicles) with an automatic magazine delivering 45 mg Noyes pellets. The boxes were equipped with a lever (5.5 cm above the grid floor) which the rat had to press to obtain reward. Electric current could be passed through the grid floor. The rats, maintained at 80–85% of their normal b. wt, were trained (16 daily sessions of 15 min) to press the lever of the Skinner box according to a continuously reinforced schedule.

Separate groups of rats were tested in the situation A or in the situation B. In the situation A, as well as in the situation B, the rats were subjected to 2 distinct experimental sessions: a session of learning with electric shocks and, 4 days later, a session of retest without shock.

'Shock-session'. Rats were individually placed in their appropriate test-apparatus, and, 30 sec later, were subjected to a contingent electric shock (situation A: 2 mA when drinking; situation B: 1 mA when pressing for food). After the electric shock, the animals remained 1 min in the apparatus and each time they drank or pressed the lever, were shocked again. Control rats with no shock, were given a 3-min placement in the apparatus without any shock.

'Test-session'. Each rat was placed for 5 min in the appropriate test-apparatus without any shock, and the time spent