The Physiology of Tremorine-Induced Tremor*

RONALD R. TASKER, M.D., AND ANDREW KERTESZ, M.D.†
Departments of Surgery (Neurosurgical Division) and Physiology, University of Toronto, Toronto, Canada

The difficulty of inducing involuntary movement in the experimental animal has been a major obstacle to the unravelling of the mechanism of human dyskinesia. The tremor induced by 1,4-dipyrrolidino-2-butyne (Tremorine, Abbott) is however one very convenient laboratory model with which to work. As Everett and his group9,10 and others14 have shown in several species, within 15 minutes of intraperitoneal injection this chemical induces rest tremor, which is inhibited by antiparkinsonian drugs, together with varying degrees of rigidity, rage, hypothermia, and cholinergic discharge. These responses have been shown to be caused by the action of the hepatic metabolite 1-(2-oxopyrrolidino)-4-pyrrolidino-2-butyne (Oxotremorine),5,20,25 and are accompanied by electrical activation of cortex, posterior hypothalamus, and dorsal hippocampus, and antagonism of strychnine-evoked potentials in the hippocampus,2 and increased rate of firing of certain mesencephalic reticular units3 with an increase in their accessibility to peripheral input. At the same time there is a reduction of brain-stem levels of norepinephrine, an increase in 5-hydroxytryptamine (rat and mouse),12 and an increase in histaminic content of corpus striatum and hypothalamus (dog).24

It is agreed that the parasympathetic effects of Tremorine are induced peripherally.6,11–13 On the other hand, although the bulk of evidence suggests that the tremor, rage and hypothermia are centrally induced16,17 not all observations support this hypothesis. In cats, the hypothalamus and midbrain have been suggested as this central site of action17–19 in rats, the mesencephalic tegmentum.16 This is difficult to reconcile with the report of Everett et al.9,10 that decerebration as well as decerebellation and hemispherectomy failed to prevent Tremorine-induced tremor. Furthermore, contrary to most studies,9,10,16,18 two have been reported to demonstrate Tremorine-induced tremor below the level of section of the spinal cord.4,22

Although the differences between human dyskinesia and Tremorine-induced tremor are well recognised it is felt that clarification of these difficulties and further elucidation of the problem of generation of one type of repetitive involuntary movement in the animal will contribute to an understanding of the human disease.

Method

Unless otherwise specified 10 mg./kg. of Tremorine* alone were injected intraperitoneally as a saline solution in each experiment. Stereotactic lesions were placed using the Baltimore Instrument Co. frame model S. Settings for the hypothalamic lesions were A 4.4 (anteroposterior) and 0.5 H (horizontal) and 2.5 V (vertical), and for the midbrain lesions, 1.0 A, 1.5 H and 2.5 V according to de Groot’s25 atlas. Thalamic lesions were made at 55 A, 80 H and 5 V according to Krieg’s24 atlas. Electrolytic lesions were made with stainless-steel needles, 0.5 mm. in diameter (0.05 × 0.1 mm. tip), coated with Glyptal varnish using the Grass model 16 lesion maker after calibration in ovalbumen. Current duration was 30 sec., at 60–80 units of intensity. Except for the preliminary studies, all others were carried out on rats of the Wistar strain. Preparations were tested postoperatively on the 2nd–3rd, and the 7th (spinal and intercollicular decerebrate) or 14th–21st days (all other). With the animal suspended horizontally in a cloth jacket, tremor was recorded on a Grass model 5 polygraph by taping to each paw a pair of 120 Ω.

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† Fellow, Medical Research Council of Canada, 1963–1964.
The restriction of tremorigensis to homeothermic vertebrates implies neurobiochemical specificities that must await further study. That this is not an hepatic problem is suggested by the failure of Oxotremorine to affect the frog.\(^7\)

Since there appears to be no published description of Tremorine-induced tremor, its characteristics in the rat will be outlined briefly. After dosages of 5–25 mm./kg., rest tremor without fatality was seen. This was a high-amplitude 13–14 c./sec. tremor, asynchronous in the 4 limbs, amplified during voluntary movement (Fig. 1) which replaced the low-amplitude 10–12 c./sec. physiological rest tremor (Fig. 3). Accompanying the tremor was a postural abnormality resembling rigidity, consisting of hyperextension of the tail, flexion of shoulder and hip, and extension of distal joints of the limbs.

**Relation to Shivering.** Because Tremorine induces hypothermia, Tremorine-induced tremor was compared with shivering, induced by wetting or cooling. That Tremorine-induced tremor is not shivering and is not the result of hypothermia was clearly shown. First of all the rate of shivering was about 25 c./sec., approximately twice that of tremor induced by Tremorine always appeared before hypothermia. Furthermore prevention of hypothermia or, alternatively, induced hyperthermia failed to prevent Tremorine-induced tremor (6 rats 38°–39°C. rectal). However reduced tremor was seen in 2 rats surviving 40°C. rectal while tremor failed to develop in 6 rats which succumbed after exposure to 40°C. or above.

The report of Patten \textit{et al.}\(^2\) hinted at similar observations on the effect of temperature. Although sensory inhibition of shivering is well known, it was found to be far less profound than that seen with Tremorine-induced tremor (see below) and the effective stimuli differed. It appears reasonable to regard the two phenomena as resulting from distinct mechanisms.

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**Results and Discussion**

**Phylogenetic Range of Tremorine.** Although Tremorine has been reported to induce tremor in mammals and birds\(^9,10\) but not in the toad,\(^2\) no report has attempted to delimit its full range of action. The domestic dove and various mammals were studied—Virginia oppossum, \textit{Didelphis virginiana}, nine-banded armadillo, \textit{Dasypus novemcinctus}, albino mouse and rat, domestic cat and dog. In all, 10–20 mg./kg. of Tremorine induced the expected effects, tremor being particularly evident in the armadillo and rodents. Enormous doses (200 mg./kg.) were without any effect in amphibia—leopard frog, \textit{Rana pipiens}, red-backed salamander, \textit{Platodon cinereus}, common newt, \textit{Diemictylus viridescens}. Violent hyperactivity, vomiting and eventual death but no tremor were seen in the reptiles—spectacled caiman, \textit{Caiman sclerops}, garter snake, \textit{Thamnophis sirtalis}, and iguana, \textit{Iguana iguana}, after 10–40 mg./kg.

![Figure 1](image-url)

**Fig. 1.** Rat 64-165. Normal rat. Left, 14 c./sec. tremor after 10 mg./kg. Tremorine. Right, shivering at 25 c./sec. Paper speed 35 mm. per sec.