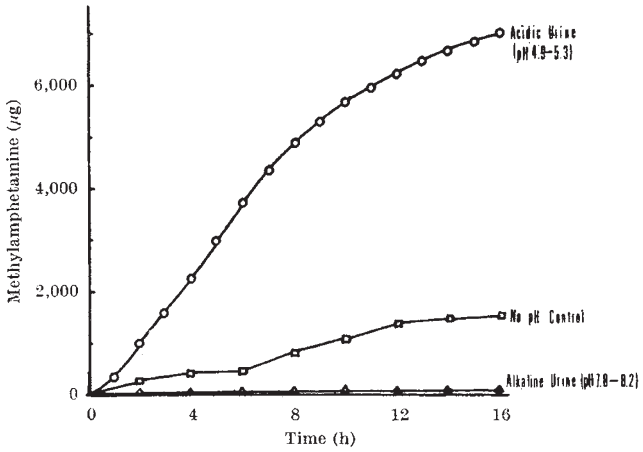

Fig. 2. Cumulative urinary excretion of methylamphetamine in man (subject M.R.) under varying conditions of urinary *p*H, after oral administration of 11·0 mg (+)-methylamphetamine

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Pharmacology of Experimental Tremor

Tremorine (1-4 dipyrolidine-2-butyn (T)) has stimulated an interest in an experimental pharmacology because it is the first substance which can definitely produce rest tremor, rigor and akinesia, that is, the symptoms of Parkinson's disease[1]. Further, the symptoms produced in tremorine-induced tremor (TT) can be relieved with all known anti-Parkinson substances and drugs inhibiting the cholinergic nervous system. Recently, Cho and Jenden[2] found that symptoms produced with (T) or with oxotremorin (oxo-T), an active principle of T, can be removed with an analogue of T, 1-4-*bis*(*N*-hexamethylenimino)-2-butyn (anti-T). T itself is the most specific substance. Everett[1] states that among many similar derivatives only T produces tremor.

Tremor can also be produced by other substances, for example, harmin[3], arecolin[4], 1-1-3-triphenyl-3-amino-propanol-1-ol (AO)[5], LSD-525 (ref. 6). Moreover, we have worked out a method of producing tremor with diethylcystamine (DEC)[4]. It was interesting to examine whether anti-T acts also on other types of tremor besides the tremor induced by T and oxo-T in order to establish the specificity of the substance as related to the structure of T.

Mice weighing 20–30 g were used. All the substances were given intraperitoneally 15 min after the application of anti-T which was also given intraperitoneally in a dose of 25 mg/kg. The animals were observed up to 60 min after the application of the substance whether they exhibited rest tremor or not. Since we have already found that T activates choline-acetylase, it was also interesting to examine the action of anti-T on this enzyme, because theoretically it can be expected as an antagonist of choline-acetylase[8,9]. We examined the action of choline-acetylase in the brain of rat by the method of Bull, Hebb, and Ratković[10]. The animals received 25 mg/kg anti-T intraperitoneally (we thank Dr. Jenden, of Los Angeles, for the supply of anti-T), and after 30 min they were killed; the brain was removed immediately, cleaned of blood and freed from its outer layer. The control groups did not receive anti-T.

Table 1

Substances which produce tremor	Dose (mg/kg)	Effect 15 min after the application of anti-T
Tremorin	25	Tremor did not develop
Oxotremorin	10	Tremor did not develop
Arecolin	20	Tremor was greatly weakened
LSD	4	Tremor did not weaken
AO	30	Tremor did not weaken
DEC	50	Tremor did not weaken
Harmin	30	Tremor did not weaken

It was thus shown that anti-T does not inhibit choline-acetylase in the rat's brain.

Table 1 shows that anti-T acts on T and oxo-T as described by Cho and Jenden[2] and it also acts on arecolin. It has no effect on LSD, DEC and AO. Since arecolin stimulates mainly muscarine receptors it is suggested that it is due to the central anti-muscarine effect and not the antagonistic action of choline-acetylase. Its effect is most probably in connexion with the block of central muscarine receptors. These findings at the same time show that tremor produced with AO, harmin, LSD and DEC is not of a cholinergic nature which can be seen to confirm the fact that tremor produced by them does not allow either atropine or other anti-Parkinson substances to accumulate. Consequently, our findings accord with the work of Cho and Jenden[2] showing that anti-T is an anticholinergic with a central action.

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Dimethylnitrosamine; its Hepatotoxic Effect in Sheep and its Occurrence in Toxic Batches of Herring Meal

During the years 1961 and 1962 there were in Norway outbreaks of toxic hepatosis in ruminants, giving rather characteristic symptoms and liver lesions[1,2]. Experiments indicated a possible connexion between the disease and the feeding of meal made from herring preserved with sodium nitrite[3]. As the hepatotoxic properties of dimethylnitrosamine have been established for several species[4,5], we decided to investigate the toxicity of this compound to sheep, and its possible occurrence in herring meal.

Toxicity experiments were performed with 7 mature ewes of two breeds. The animals were fed hay and concentrates *ad libitum*. Dimethylnitrosamine (supplied by Eastman Organic Chemicals, Rochester, N.Y.) was diluted with water and administered by stomach tube. Hepatic tests were carried out as previously described[1]. Gross pathological and histological examinations were performed as in ref. 2. The dosages given to each animal are listed in Table 1, together with the time which elapsed from the beginning of each experiment until appearance of symptoms and until death.