quantity initiates uterine growth, a considerable increase of dosage augments this growth only slightly(5). 3. Hisaw *et al.*(6) discovered that estriol can reduce the effectiveness of estrone in promoting uterine growth when these steroids are injected together.

Evidence has been presented that these physiologic properties of estriol are due to the interaction of its 16α-hydroxyl group with that specific protein surface of the uterine cell which is of critical importance in promoting growth. It would appear from the present experiments that progesterone can block the inhibitory action of this hydroxyl group when small amounts of estriol are present and so enhance the growth promoting activity of the phenolic group in the molecule.

Conclusions. 1. Whereas progesterone inhibits the growth promoting action of estrone on the uterus of hypophysectomized rats, its effects on estriol-induced growth are biphasic. 2. Progesterone depresses uterine growth evoked by large quantities of estriol but *enhances* growth promoting action of small quantities of this impeded estrogen.

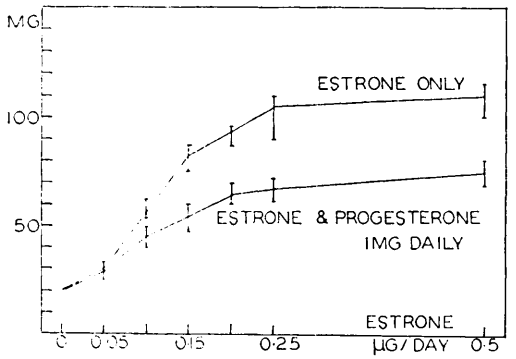

FIG. 1. Effect of progesterone, 1 mg daily, on growth of uterus induced by estrone. Ordinates: wt of uterus. Abscissae: daily dosage of estrone.

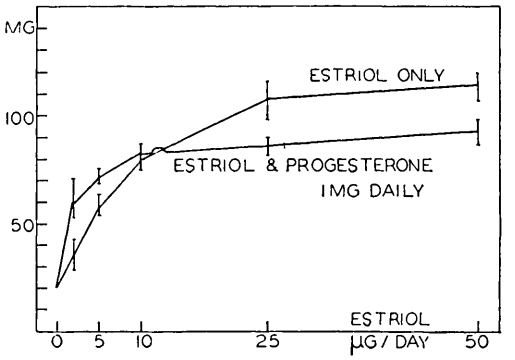

FIG. 2. Effects of progesterone, 1 mg daily, on growth of uterus induced by estriol. With smaller quantities of estriol, growth is enhanced but with larger quantities it is inhibited. Ordinates: wt of uterus. Abscissae: daily dosage of estriol.

1. Hertz, R., Larsen, C. D., and Tullner, W., *J. Nat. Cancer Inst.*, 1947, v8, 123.

2. Huggins, C., and Jensen, E. V., *J. Exp. Med.*, 1955, v102, 335.

3. ———, *ibid.*, 1955, v102, 347.

4. Curtis, J. M., and Doisy, E. A., *J. Biol. Chem.*, 1931, v91, 647.

5. Dorfman, R. I., PROC. SOC. EXP. BIOL. AND MED., 1940, v45, 594.

6. Hisaw, F. L., Velardo, J. T., and Goolsby, C. M., *Fed. Proc.*, 1953, v12, 68.

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Anticonvulsant Effect of Morpholinethylmorphine. (22459)

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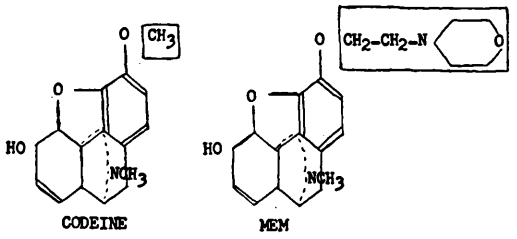
Morpholinethylmorphine (MEM)* is an amino alkyl ether of morphine resulting from substitution of morphine's phenolic hydrogen by the morpholinethyl radical. It was prepared by Chabrier, *et al.*(1) and described as an anti-tussive agent which possessed neither the convulsant effect nor the smooth muscle stimulating action of codeine. The close structural relationship of MEM to codeine

* Obtained from Dr. R. Giudicelli, Dausse Laboratories, Paris, France.

(methylmorphine) is shown below.



The present investigation is concerned with a comparison of the central depressant effect of MEM with that of codeine, some synthetic morphine analogues (methadone isomers), Miltown, and chlorpromazine.

Materials and methods. 300 Webster female albino mice (18 to 25 g), 450 Wistar female albino rats (100 to 125 g), and 15 adult mongrel dogs of both sexes were used. Presence or absence of central depressant effect in mice and rats was determined by observation of running movements, restlessness, convulsions, incoordination, and loss of righting reflex. In dogs the appearance of miosis, bradycardia, emesis, and convulsions were noted. The prolongation of hexobarbital hypnosis in mice and dogs was observed by noting the time of loss of the righting reflex; control animals were treated with saline before hexobarbital administration. Effects of drugs on pentylenetetrazole induced convulsions in rats were determined by a previously described technic(2). Anticonvulsant effects were studied against 2 dose levels of pentylenetetrazole, 75 mg/kg (LD_{35}) and 100 mg/kg (LD_{100}), both doses producing convulsions in 100% of the untreated rats. The incidence of convulsions and death in 10 rats receiving the anticonvulsant ½ hour before pentylenetetrazole was compared with the incidence in 20 control rats which received pentylenetetrazole alone.

Results. Effects on C.N.S. Doses of MEM in mice up to 480 mg/kg subcutaneously (s.c.) and 900 mg/kg orally did not produce depressant or stimulant effects, loss of righting reflex, or catatonus of the tail. The incidence of convulsions was very low even at the toxic oral dose of 640 mg/kg. On the other hand, codeine in mice at doses from 90 to 180 mg/kg intraperitoneally (i.p.) produced restlessness, tail catatonus, and convulsions. Ketobemidone and dl-Methadone, both at 6 mg/kg i.p., induced a very moderate restlessness in mice, and Miltown induced paralysis and loss of righting reflex at 200 to 400 mg/kg s.c. In rats MEM produced no effects until a dose of 300 mg/kg s.c. was given, which produced relaxation and flaccidity. In dogs no effect was observed up to 150 mg/kg s.c., but 300 mg/kg induced ataxia, general depression, and tran-

TABLE I. Prolongation of Hexobarbital Sodium Hypnosis. (100 mg/kg i.p.) by previous administration of MEM, codeine, and chlorpromazine.

Exp. No.	Drug	Dose	Route of admin.	Time before hexobarbital (min.)	Mean duration of hypnosis (min.) ± S.E.	t	P
I	Saline	.1 cc/10 g	S.C.	30	19 ± 2.36	—	—
	MEM	75 mg/kg	"	"	26 ± 3.50	1.67	.1
	"	150 "	"	"	53 ±10.15	3.27	<.01
	Codeine (ph^{te})	15 "	"	"	32 ± 5.40	2.20	.04
II	Saline	.1 cc/10 g	"	"	31 ± 2.61	—	—
	MEM	300 mg/kg	"	60	61 ± 5.63	4.84	<.01
	"	300 "	Oral	"	43 ± 6.01	1.84	.09
	Codeine (ph^{te})	30 "	S.C.	"	61 ± 7.64	3.72	<.01
III	Saline	.4 cc/10 g	Oral	"	40 ± 4.86	—	—
	MEM	300 mg/kg	"	30	55 ± 6.83	1.78	.1
	"	600 "	"	"	65 ± 8.32	2.60	.02
	Codeine (ph^{te})	600 "	"	60	60 ± 8.83	1.98	.06
IV	Saline	.1 cc/10 g	S.C.	30	26 ± 3.54	—	—
	Chlorpromazine	.5 mg/kg	"	"	31 ± 4.48	.88	.42
	"	1 "	"	"	41 ± 4.40	2.68	.02
	"	5 "	"	"	88 ± 7.45	7.96	<.01

10 mice used for each experiment. S.E. = Stand. error of mean.

sient bradycardia. Codeine in dogs induced excitement and convulsions at 75 mg/kg s.c. and was fatal at 150 mg/kg.

Prolongation of hexobarbital sleep. The results of these experiments in mice are shown in Table I. It can be seen that doses of MEM which were not depressant in themselves significantly increased the hypnotic effect of hexobarbital sodium. The extent of the effect was related to magnitude of dose. The hypnotic effect of MEM was no greater than that of codeine or chlorpromazine. A prolongation of hexobarbital hypnosis was also observed in dogs with MEM 30 mg/kg s.c. and with codeine 7.5 mg/kg s.c. given ½ hour before hexobarbital 50 mg/kg intravenously (i.v.).

Effect on pentylenetetrazole induced convulsions. Fig. 1 shows that MEM was strikingly effective in protecting rats from convulsions induced by 75 mg/kg pentylenetetrazole; the ED_{50} for MEM was 200 mg/kg. A good anticonvulsant effect was also noted with Miltown 30 to 120 mg/kg, confirming Berger's data(3) with mice. On the other hand, morphine, dl-Methadone, l-Methadone, ketobemidone, codeine, l-Isomethadone, and Meperidine were all ineffective, although a trend towards protection was seen with small doses of the latter 3 drugs. Morphine also had a fair anticonvulsant action at the smaller dose of 3 mg/kg. MEM effectively antagonized the convulsions induced by 100 mg/kg pentylenetetrazole, the ED_{50} in this case being 450 mg/kg.

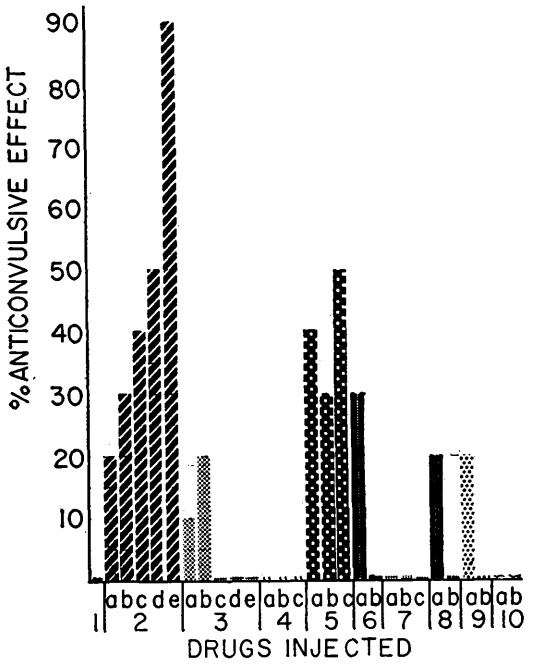


FIG. 1. Effect of various drugs (mg/kg) in antagonizing convulsions in rats induced by pentylenetetrazole 75 mg/kg i.p.: (1) Controls; (2) MEM: a. 50, b. 150, c. 200, d. 300, e. 450; (3) codeine phosphate: a. 5, b. 10, c. 15, d. 30, e. 315; (4) dl-Methadone: a. 3, b. 10, c. 30; (5) Miltown: a. 30, b. 60, c. 120; (6) morphine sulfate: a. 3, b. 30; (7) ketobemidone: a. 1.5, b. 5, c. 15; (8) Meperidine HCl: a. 30, b. 300; (9) l-Isomethadone: a. 3, b. 30; (10) l-Methadone: a. 1.5, b. 15.

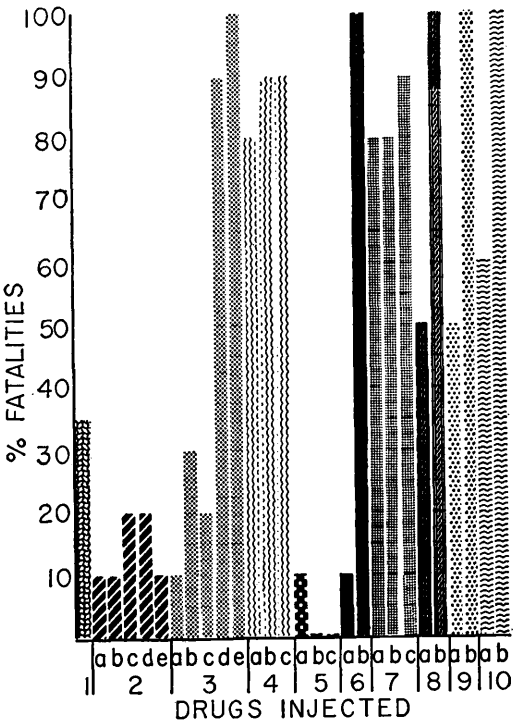


FIG. 2. Effect of various drugs (mg/kg) in rats on mortalities induced by pentylenetetrazole 75 mg /kg i.p.: (1) Controls; (2) MEM: a. 50, b. 150, c. 200, d. 300, e. 450; (3) codeine phosphate: a. 5, b. 10, c. 15, d. 30, e. 315; (4) dl-Methadone: a. 3, b. 10, c. 30; (5) Miltown: a. 30, b. 60, c. 120; (6) morphine sulfate: a. 3, b. 30; (7) ketobemidone: a. 1.5, b. 5, c. 15; (8) Meperidine HCl: a. 30, b. 300; (9) l-Isomethadone: a. 3, b. 30; (10) l-Methadone: a. 1.5, b. 15.

Effect on pentylenetetrazole toxicity. MEM 25 to 450 mg/kg s.c. in rats was very effective in preventing the lethal effects of LD_{35}

and LD_{100} pentylenetetrazole, as shown in Fig. 2. The effectiveness of Miltown in this respect again confirms Berger's data with mice(3). However, methadone isomers and high doses of morphine and codeine significantly potentiated pentylenetetrazole toxicity, while the low doses of the latter 2 drugs were protective.

Discussion. The results of these experiments show clearly that MEM, unlike morphine, codeine, and methadone isomers, is devoid of a central excitatory action in non-toxic doses in the 3 species studied. It is for this reason that MEM significantly protects against pentylenetetrazole convulsions and fatalities, while morphine, codeine, and the methadones potentiate these effects. However, we have found that smaller doses of these latter compounds, in contradiction to the data of Hazelton and Koppanyi(4,5), are also protective against the effects of pentylenetetrazole; these doses probably produce only C.N.S. depression without a simultaneous stimulatory action.

Summary. (1) In non-toxic doses MEM shows no C.N.S. excitatory effects in mice, rats, and dogs. (2) In doses which do not induce loss of righting reflex, MEM prolongs hexobarbital hypnosis. (3) MEM, unlike morphine, codeine, and some methadone isomers, significantly blocks the convulsant and toxic effects of pentylenetetrazole.

1. Chabrier, P., Giudicelli, R., and Thuillier, J., *Ann. Pharm. Fran.*, 1950, v8, 261.
2. Cahen, R. L., *J. Pharmacol. Exp. Therap.*, 1946, v88, 343.
3. Berger, T., *ibid.*, 1954, v112, 413.
4. Hazelton, L. W., and Koppanyi, T., *ibid.*, 1940, v69, 290.
5. ———, *Anesthesiology*, 1941, v2, 427.

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Frequency of t^w Alleles in a Confined Population of Wild House Mice.* (22460)

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The T locus in mice represents a complex locus in which 11 reported alleles, many of them proven to be different from others, have been derived from laboratory stocks. Many populations of wild mice have also been shown to contain recessive mutants at the T locus. Some of these wild alleles have been shown to be different from those found in laboratory stocks(1). The dominant allele, T, is homozygous lethal and when present in heterozygous condition, T +, with the normal allele causes a variable shortening of the tail (Brachury = short tail). In addition to T there is a series of recessive alleles, t^n, each of which when present with T (as T/t^n) produces the tailless phenotype. The recessive alleles, t^n, may be homozygous lethal or viable. When viable, the males of the genotype, t^n/t^n, are usually sterile. Viable female mice of the genotype, t^n/t^n, are usually fertile. It is relatively simple to discover whether a mouse has the genotype $+/t^n$ or $+/+$. The animal in question is mated to a Brachy ($T/+$). If the animal in question is $+/+$ only two types of offspring are obtained: normal tailed and Brachy, in approximately equal numbers. Should the mouse in question, however, be $+/t^n$, then 3 classes of offspring are found; namely, normal tailed, Brachy and tailless. This latter group has the genotype, T/t^n. Provided that sufficient numbers of offspring are obtained from a test animal, it can be classified as $+/+$ or $+/t^n$. In males the procedure is greatly aided by the phe-

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