the strength or amplitude of the mandibular movements was somewhat reduced in the early phase of the second series. The duration of individual gasps was always shorter the greater the frequency of gasping.

Although the total expenditure of energy has not been accurately determined, it is apparent that morphine, alcohol, urethane, chloralose and cyclopropane definitely increase the over-all energy liberation. The mechanism involved in this additional energy liberation is being studied.

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Ejaculation Induced by a Uterine Drug (Gravitol)

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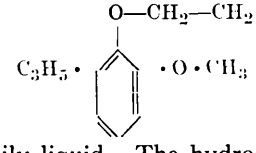
Gravitol is the di-ethyl-amino-ethyl-ether of 2-methoxy-6-allyl-phenol. The base itself



is a thin oily liquid. The hydrochloride is a crystalline water-soluble substance. For the purposes of this investigation the 1% aqueous solution of the hydrochloride was used. Gravitol, also on the market with the trade names Clavitol and Uterol, has been introduced as a uterine drug.[1] Significant stimulating as well as depressing actions upon uterus, intestine, blood vessels and blood pressure were previously described by Barkan and his associates.[2-6] Pharmacological observations were also reported by Anan[7] and Okazaki.[8] A discussion on the drug's action upon the heart went on between van Dongen and Bijlsma[9-11] on the one hand and de Boer[12,13] on the other. Regarding the action upon the heart Jackson[14] published extremely interesting observations. As far as the general toxicity is concerned[4] there is a definite combination and alternation of both central stimulation culminating in convulsions, and depression with motor paralysis. Following preliminary observations made in collaboration with E. Käer, it was found that among the signs of stimulation the most consistent action is the ejaculation induced by the drug in male guinea pigs.†

Procedure. Mature male guinea pigs varying in weight between about 500 and 900 g were kept on a mixed diet. After some days of acclimatisation they were used for the experiments. Subcutaneous injections with 1% Gravitol solution were made in 7 different doses, from 10 to 50 mg per

* Partially aided by The Rockefeller Foundation.

1 Eichholtz, F., *Münch. med. Wschr.*, 1928, **75**, 1281.

2 Barkan, G., *Münch. med. Wschr.*, 1932, **79**, 871.

3 Barkan, G., *Arch. f. exp. Path. u. Pharmakol.*, 1932, **167**, 84.

4 Käer, E., and Barkan, G., *Arch. f. exp. Path. u. Pharmakol.*, 1933, **170**, 111.

5 Barkan, G., Prikk, S., and Dreyblatt, R., unpublished.

6 Kingisepp, G., *Arch. f. exp. Path. u. Pharmakol.*, 1935, **177**, 587.

7 Anan, Shinji, *Fol. jap. pharmacol.*, 1929, **9**, 53.

8 Okazaki, Tadashi, *Jap. J. med. Sci.*, IV. Pharmacol., 1932, **6**, 23.

9 van Dongen, K., *Arch. internat. Pharmacodynamie*, 1936, **53**, 80.

10 Bijlsma, U. G., and van Dongen, K., *Arch. internat. Pharmacodynamie*, 1937, **55**, 257.

11 Bijlsma, U. G., and van Dongen, K., *Arch. internat. Pharmacodynamie*, 1937, **55**, 265.

12 de Boer, S., *Arch. internat. Pharmacodynamie*, 1936, **54**, 65.

13 de Boer, S., *Arch. internat. Pharmacodynamie*, 1937, **55**, 262.

14 Jackson, D. E., *Experimental Pharmacology and Materia Medica*, 2d Ed., 1939, St. Louis.

† A preliminary report has been presented before The American Society for Pharmacology and Experimental Therapeutics, Boston Meeting, April, 1942.

kg of body weight. From previous experiments[4] the last dose was known to be lethal in about 50% of the animals. Between 6 and 13 animals were used in each group of dosage.

Results. Ten mg of Gravitol per kg of body weight were entirely ineffective. With larger doses an increased percentage of the animals showed ejaculation. In almost all of the experiments with ejaculatory response living spermatozoa were found, and there was also the typical coagulation of the ejaculate *in situ,* caused by the known action of the prostatic enzyme vesiculase.[15] Only in a very few instances one of the two phenomena was missing, *i.e.,* there were spermatozoa present but no coagulation, or coagulation occurred but no spermatozoa were found under the microscope. Table I shows the results obtained in 59 experiments, 37 of which were positive in the named respect.

TABLE I.
Frequency of Ejaculatory Response of Male Guinea Pigs with Varying Subcutaneous Doses of Gravitol.

Gravitol subc. mg per kg	10	20	25	30	35	40	50
No. of animals tested	6	7	6	7	13	13	7
No. of animals responding	0	1	2	5	10	12	7
Frequency of ejaculation, %	0	14.3	33.3	71.4	76.9	92.4	100

Applying Kärber's[16] method of mathematical treatment to the experimental results, 27.9 mg per kg of body weight were calculated as the dose which would show an ejaculatory response in 50% of the animals. Plotting the dose, or the log of the dose, against the frequency of positive effect typical S-curves are obtained. By graphical interpolation, either on these S-curves, or on the straight line obtained in substituting the percentage of positive response by the normal equivalent deviation,[17] between 27 and 28 mg of Gravitol per kg of body weight was found to be the 50% effective dose in guinea pigs, in good agreement with the above calculated value.

Table I (and the curve constructed from the tabulated data) shows definitely that the ejaculatory effect of the drug is a specific one. In all instances the ejaculation is intravital, occurring within 10 min to one hr after injection. Only once the effect was noticed after 7 min and once after more than one hr (66 min). Incidentally in both instances the dose of 40 mg per kg body weight had been injected. This in accordance with other observations indicates that the latent period between injection of the drug and ejaculation is not dependent upon dosage. In many experiments, particularly with larger doses, repeated ejaculations were observed. With 40 mg per kg more than 90% of the animals recover within 1 to 2 hr (only one lethal effect out of 13 cases). After a few days' rest the guinea pigs can be used again.

Utilizing this fact the consistency of the sensitivity in the same guinea pig on subsequent administrations was tested in a series of experiments. The examples listed in Table II would show that the individual sensitivity to the drug with respect to the ejaculatory response, though varying from animal to animal, is rather consistent in the same animal.

TABLE II.
Ejaculatory Response of the Same Guinea Pig to Repeated Administration of Gravitol.
(Doses per kg body weight)

Guinea pig No.	First experiment	Second experiment	Third experiment
142	25 mg positive	25 mg positive	25 mg positive
147	40 mg positive	35 mg positive	25 mg negative
149	40 mg negative	35 mg negative	50 mg positive

It might be mentioned that identical effects could be brought about by intragastric administration of tenfold doses; 200 mg per kg was the lowest dose which on gastric application caused ejaculation.

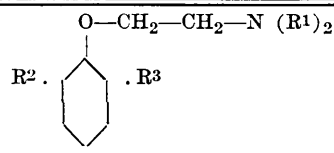
A few informatory experiments were car-

[15] Camus, L., and Gley, E., *C. R. Soc. Biol.,* 1897, p. 787.

[16] Kärber, G., *Arch. f. exp. Path. u. Pharmacol.,* 1931, **162,** 480.

[17] Hemmingsen, A. M., *Quart. J. Pharm. Pharmacol.,* 1933, **6,** 39.

TABLE III.
Positive and Negative Ejaculatory Response of Guinea Pigs to Gravitol Homologs.



	Positive.				
R^1:	C_2H_5	C_2H_5	C_2H_5	C_2H_5	C_3H_5
R^2:	C_3H_5 (allyl)	$CH_3CH{=}CH$	C_3H_5	C_4H_7	OCH_3
R^3:	OCH_3 Gravitol	OCH_3	OC_2H_5	OCH_3	OCH_3
	Negative.				
R^1:	C_2H_5	C_3H_5	C_3H_5	C_3H_5	C_3H_5
R^2:	C_3H_5	C_4H_7	C_3H_5	$COOCH_3$	C_3H_5
R^3:	$COOCH_3$	OCH_3	—	OCH_3	OC_2H_5

ried out with some homologs of Gravitol. The results shown in Table III are qualitatively grouped as positive and negative depending on whether or not there was any ejaculatory response to subcutaneous injection of the respective hydrochlorides in any dosage in guinea pigs. None of the derivatives listed as positive reached the effectiveness of the original drug. The experience in this respect, however, is definitely incomplete and of purely preliminary nature. Yet, even with this limitation, the synopsis might be of some value for further study concerning the dependence of ejaculatory effect on chemical structure.

Discussion. Although in most of the positively reacting cases convulsions did occur, the convulsions obviously are not the dominating but rather a coördinated effect in the ejaculatory response to Gravitol. The reasons for this conclusion are:

(1) There were instances, particularly with the smaller doses of Gravitol, in which convulsions did not develop but only signs of minor central stimulation, and yet the ejaculatory response occurred.

(2) In other cases in which convulsions did develop later, the ejaculation occurred prior to the convulsions.

(3) With a superficial ether-anesthesia convulsions could be avoided or suppressed without abolishing the ejaculatory effect. Also with a barbiturate the same was found to be true; 30 to 40 mg of sodium amytal per kg guinea pig given subcutaneously produced anesthesia and sleep for almost 3 hr. Gravitol when injected in doses of 40 mg per kg during full anesthesia (½ to 1 hr after the injection of the hypnotic) was ineffective. The same guinea pigs, however, a few days later, when given even a smaller dose of Gravitol (30 mg per kg), but 7 to 10 min after sodium amytal, reacted while narcotized with typical ejaculation without convulsion or motor stimulation.

A few years ago Loewe[18-20] demonstrated that certain combinations of hypnotics and stimulants will cause prompt ejaculation in albino mice. It is interesting, as may be stated again, that the drug here studied shows both depressing and stimulating actions on the central nervous system.[4] It seems probable that these two actions incidentally combined in one single drug are responsible for the ejaculatory effect. The site of central stimulation causing the ejaculatory reflex is most likely identical with the one in the ejaculation produced by electric stimulation of the brain of the lightly anesthetized guinea pig.[21-23]

Summary. 1. The di-ethyl-amino-ethyl-ether of 2-methoxy-6-allyl-phenol in form of its hydrochloride (Gravitol, Clavitol, Uterol) was found to elicit a characteristic ejaculatory reflex in the mature male guinea pig.

2. This characteristic effect is attributed to the previously studied combination of the drug's depressing and stimulating action upon the central nervous system.

[18] Loewe, S., PROC. SOC. EXP. BIOL. AND MED., 1937, **37**, 483.

[19] Loewe, S., *J. Pharmacol. and Exp. Therap.*, 1938, **63**, 70.

[20] Loewe, S., *Arch. internat. Pharmacodynamie*, 1938, **60**, 37.

[21] Batelli, F., *C. R. Soc. de physique et d'histoire naturelle de Geneve*, 1922, **39**, 73.

[22] Moore, C. R., and Gallagher, T. F., *Am. J. Physiol.*, 1929, **89**, 388.

[23] Moore, C. R., and Gallagher, T. F., *Am. J. Anat.*, 1930, **45**, 39.