SCIENTIFIC SECTION

THE ACTION OF ERGOT AND ITS ALKALOIDS ON THE PUERPERAL UTERI OF DOGS.*[1]

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Since the isolation of the alkaloids, ergotoxine by Carr and Barger (1) in 1906 and ergotamine by Stoll (2), (3), (4) in 1920, the subject of ergot has been the source of considerable investigation. Of distinct interest is the more recent work of Moir (5), who has shown clinically that ergotoxine is just as effective as ergotamine. Moir (6) in the continuation of his clinical study, observed an effect with the fluidextract, when given by mouth, that has a much more rapid onset of action on the puerperal uterus than either ergotoxine or ergotamine.

In our comparative pharmacological study of the fluidextract of ergot and its active principles by the various well-known methods the intact puerperal uterus of dogs has been helpful as a method of test.

This method is based on the use of intact dog uteri, three to six days post-partum. Under ether anesthesia, an elongated rubber balloon or bag (five inches long and one and one-half inches in diameter) is inserted through the vagina into either the right or left fallopian tube. For definite location of the balloon in the uterine horn, an abdominal incision is made. The balloon is attached to a tambour by a rubber tube. Before each experiment this closed system is tested for leaks.

In these experiments more than a hundred dogs were used. The drugs were given by vein and by mouth in doses distinctly larger than that used by Moir (5), (6).

Clinically, Moir (5) has shown that ergotoxine or ergotamine in doses of 1 mg. to 3 mg. by mouth produces slow and erratic results on the uterus. The onset of action is delayed for thirty-five minutes to one hour or more. For the fluidextract or liquid extract B. P. 1914 given orally in doses of 2 to 4 drachms, Moir (6) observed that the onset of action on the uterus is strikingly shorter than that of the alkaloids.

As shown in Table I, by the U. S. P. Cock's Comb and Reversal Uteri Methods the various preparations, with the exception of the liquid extract of ergot B. P., have approximately the same potency.

By vein, as shown in Table II, the onset of action is approximately the same for the fluidextract, liquid extract B. P. 1914, ammonia extract, acetone extract, ether extract, ethylene dichloride extract, sulphur dioxide extract and alkaloids ergotoxine or ergotamine. With doses of 0.2 cc. per Kg. of the fluidextract U. S. P., the liquid extract B. P. 1914, 0.1 mg. of the various extracts or 0.1 mg. per Kg. of the alkaloids, the onset of action on the uterus is one to one and one-half minutes.

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* Scientific Section, A. PH. A., Madison meeting, 1933.

[1] This paper was passed by the Board of Review on Papers and returned to the authors for addition of kymographic tracings.—*Editor.*

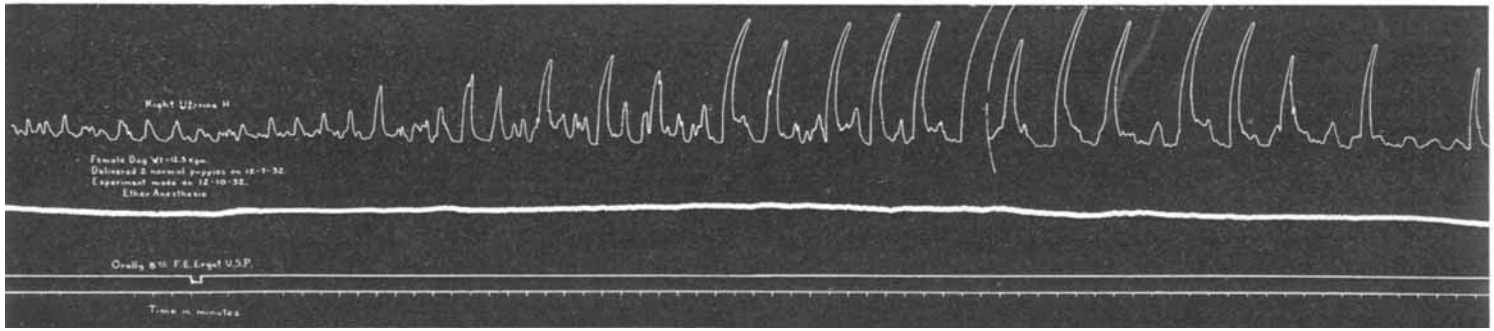

Fig. 1.—Represents an etherized dog with recorded puerperal uterine contractions. Fluidextract ergot U. S. P., 0.65 cc. per Kg. was given by mouth. In ten minutes the uterus began to show increase in contractions. These contractions increased in amplitude and remained strong for more than sixty minutes.

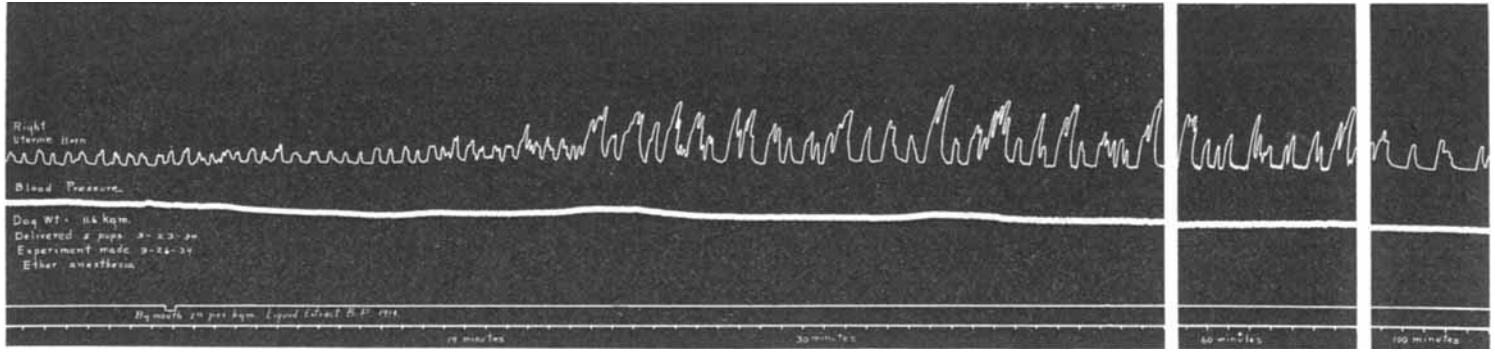

Fig. 2.—An etherized dog with recorded blood pressure and puerperal uterine contractions. Liquid extract of ergot B. P. 1914, 2 cc. per Kg. was given by mouth. In fourteen minutes the contractions of the uterus began to show stimulation. The contractions were strong for more than one hundred minutes.

Thus, by vein, the time of onset of action for the alkaloids is the same as that of the fluidextract of ergot U. S. P., the liquid extract of ergot B. P. 1914 or the various extracts.

By mouth as shown in Table III, the onset of action of the fluidextract of ergot U. S. P., liquid extract of ergot B. P. 1914, various extracts of ergot (ammonia, acetone, ether, ethylene dichloride and sulphur dioxide) is more rapid than that of the alkaloids ergotamine or ergotoxine. With a standard fluidextract of ergot U. S. P. in doses of 0.2 cc. to 1 cc. per Kg. (equivalent to 0.1 mg. to 0.5 mg. per Kg. of the alkaloids) the onset of definite response is eight to twenty

TABLE I.

Preparation.	U. S. P. Cock's Comb Method.	Reversal Uteri Method.
Fluidextract Ergot U. S. P.	100%	100%
Liquid Extract of Ergot B. P. 1914	25%	40% to 50%
Ammonia Extract of Ergot	100%	90%
Acetone Extract of Ergot	...	100%
Ether Extract of Ergot	...	90%
Ethylene Dichloride Extract of Ergot*	110%	112%
Sulphur Dioxide Extract of Ergot*	100%	80%
Ergotamine Tartrate Sandoz	100%	100%
Ergotoxine Ethanesulphonate	110%	120% to 130%

* Process patent applied for.

TABLE II.—PUERPERAL UTERI OF DOGS, INTRAVENOUS ADMINISTRATION.

Dog No.	Body Weight, Kg.	Number of Days, Post-partum.	Drug.	Dose in Cc. or Mg. per Kg.	Time of Onset of Definite Response, Minutes.	Duration of Action, Minutes.	Remarks, Contractions.
1	8.5	5	Fluidextract of Ergot U. S. P.	0.2 cc.	1.5	40	Strong
2	15.0	4	Liquid Extract of Ergot B. P. 1914	0.2 cc.	1.0	25	Strong
3	9.8	4	Ergotoxine	0.2 mg.	1.0	30	Strong
4	8.9	5	Ergotamine	0.1 mg.	1.5	35	Strong
5	16.5	4	Ammonia Extract of Ergot	0.1 mg.	1.0	50	Very strong
6	15.0	3	Acetone Extract of Ergot	0.1 mg.	1.5	15	Fair
7	13.5	4	Ether Extract of Ergot	0.1 mg.	1.5	25	Fair
8	17.0	4	Ethylene Dichloride Extract of Ergot	0.1 mg.	2.0	30	Strong
9	9.2	3	Sulphur Dioxide Extract of Ergot	0.1 mg.	1.0	50	Very strong

minutes. In doses of 2 cc. per Kg. (equivalent to 0.5 mg. per Kg. of ergotamine as determined by the Reversal Uteri Method or the U. S. P. Cock's Comb Method) the time of onset of action with the liquid extract B. P. 1914 is about ten to twenty minutes. As shown in Table III, the various extracts of ergot (ammonia, acetone, ether, ethylene dichloride and sulphur dioxide) in doses of 0.1 mg. to 1 mg. per Kg. (equivalent to ergotamine as determined by the Reversal Uteri and U. S. P

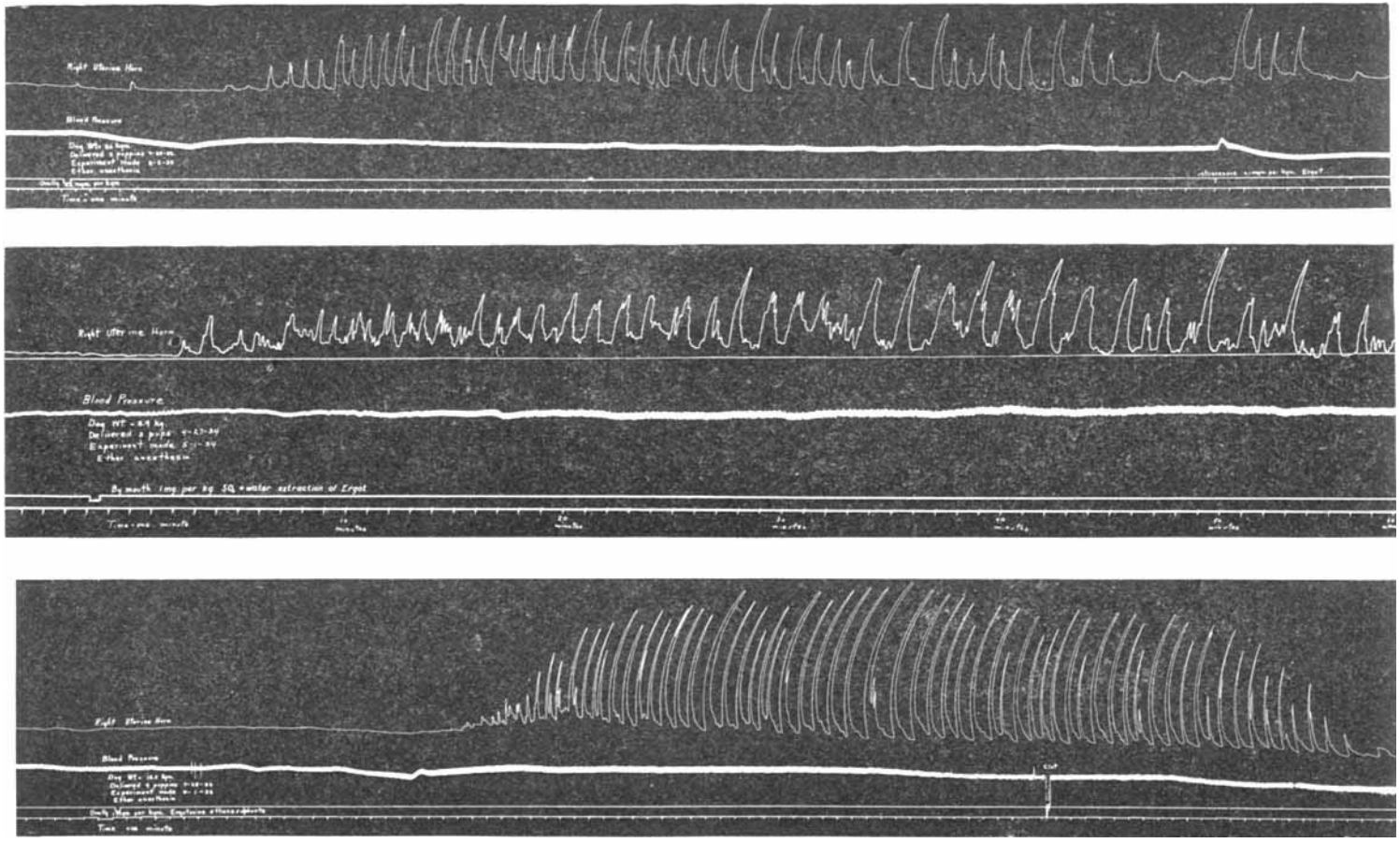

Fig. 3.—Represents a dose of 0.2 mg. per Kg. of the ammonia extract by mouth. There was definite response of contraction of uterus in thirteen minutes. Fig. 4.—Represents an etherized postpartum dog with uterine contractions. The sulphur dioxide extract by mouth produced definite response of contraction of uterus in five minutes. Fig. 5.—An etherized dog with recorded blood pressure and puerperal uterine action. Ergotoxine ethanesulphonate 1 mg. per Kg. was given by mouth. In thirty minutes the contractions of the uterus began to show effects of the ergot. The contractions were very strong for more than sixty minutes.

Cock's Comb Methods) produce definite response of action by mouth in four minutes to fifteen minutes. Thus, by mouth, the fluidextract of ergot U. S. P., liquid extract of ergot B. P. 1914, or the various extracts of ergot as shown in Table III, have approximately the same time of onset of action on the puerperal uteri of dogs.

As shown in Table III, with ergotamine in doses of 0.4 mg. to 1 mg. per Kg. the time of definite response is forty to fifty minutes. In doses of 0.5 mg. to 1 mg. per Kg. with ergotoxine definite action is shown in thirty to sixty minutes. Thus, both ergotamine or ergotoxine have a more prolonged definite onset of response on the puerperal uteri of dogs than that of the fluidextract of ergot U. S. P., liquid extract of ergot B. P. 1914 or the extracts of ergot (ammonia, acetone, ether, ethylene dichloride and sulphur dioxide).

TABLE III.—PUERPERAL UTERI OF DOGS, ORAL ADMINISTRATION.

Number of Dog.	Body Weight, Kg.	Number of Days, Post-partum.	Drug.	Dose in Cc. or Mg. per Kg. Cc.	Time of Onset of Doubtful Response, Minutes.	Time of Onset of Definite Response, Minutes.	Duration of Action, Minutes.	Remarks, Contractions.
10	19.4	4		0.2	..	8	40	Weak
11	7.1	3		0.5	..	12	30	Strong
12	12.3	3		0.65	5	10	90	Powerful
13	14.1	6	Fluidextract	0.70	4	20	40	Strong
14	8.0	5	Ergot U. S. P.	1.00	4	8	60	Strong
15	12.0	4		1.00	10	15	70	Strong
16	11.9	4		1.00	..	10	50	Strong
17	14.8	4		1.00	6	12	100	Strong
18	10.0	4		1.00	None	None	None	No response
19	24.0	3	Liquid Extract	2.00	..	10	60	Strong
20	11.6	3	of Ergot B. P.	2.00	10	14	120	Strong
21	8.4	4	1914	2.00	10	20	50	Strong
22	15.0	4		2.00	9	16	40	Strong
23	16.8	3		0.10	None	None	None	No response
24	11.0	5		0.20	None	None	None	No response
25	11.0	4		0.20	..	50	30	Weak
26	5.0	4	Ergotamine Tar-	0.40	..	40	50	Weak
27	8.0	3	trate	0.50	..	60	40	Weak
28	8.1	3		0.60	..	45	70	Strong
29	8.1	4		1.00	10	48	60	Strong
30	10.0	5		1.00	..	55	50	Strong
31	12.7	3		0.20	None	None	None	No response
32	3.9	6		0.50	..	40	30	Weak
33	11.7	5		0.50	..	60	30	Weak
34	12.5	4	Ergotoxine	0.50	..	50	30	Strong
35	18.4	6	Ethanesul-	1.00	25	30	60	Powerful
36	8.2	5	phonate	1.00	..	40	30	Strong
37	10.2	4		1.00	..	30	40	Strong
38	13.0	3		1.00	..	50	50	Strong
39	22.4	4		1.00	..	40	120	Powerful
40	14.6	4		0.07	None	None	None	No action
41	13.4	5		0.08	None	None	None	No action
42	14.0	4		0.10	..	4	30	Weak
43	10.5	4		0.10	..	8	40	Strong

TABLE II.—*Continued.*

44	12.6	5		0.15	None	None	None	Leak in system
45	15.6	4	Ammonia Extract of Ergot	0.20		5	40	Strong
46	15.2	4		0.20	None	None	None	Leak in system
47	8.6	4		0.20	10	13	60	Strong
48	8.6	3		0.25	..	10	30	Strong
49	14.2	4		0.50	..	8	50	Powerful
50	16.5	5		0.50	..	10	50	Powerful
51	9.5	4		0.60	5	15	60	Powerful
52	13.5	4		1.00	..	9	30	Powerful
53	14.0	4	Acetone Extract of Ergot	1.00	5	10	35	Fair
54	11.5	3	Ether Extract of Ergot	1.00	8	13	45	Fair
55	10.0	3	Ethylene Dichloride Extract of Ergot	1.00	10	14	40	Strong
56	13.0	4		1.00	10	12	30	Fair
57	8.7	3		1.00	9	15	120+	Powerful
58	10.6	3	Sulphur Dioxide Extract of Ergot	1.00	3	4	30	Strong
59	12.4	3		1.00	3	4	40	Strong
60	8.9	4		1.00	3	5	60+	Powerful

CONCLUSIONS.

1. As a pharmacological method the intact puerperal uteri of dogs is helpful in the study of the active principles of ergot.

2. On the puerperal uterus the fluidextract of ergot U. S. P., liquid extract of ergot B. P. 1914 and the various extracts by mouth show a more rapid onset of definite contractions than that of the alkaloids, ergotamine or ergotoxine.

3. Ergot contains a principle (not ergotamine or ergotoxine) that produces by mouth a rapid onset of action on the puerperal uterus of dogs.

REFERENCES.

(1) F. H. Carr and G. Barger, "Note on Ergot Alkaloids," *Chem. News*, 94 (1906), 89.

(2) A. Stoll, "Zur Kenntnis der Mutterkornalkaloid," *Verhandl. Schweiz. Naturl. Gesellsch.* (1920), 190.

(3) K. Spiro and A. Stoll, "Ueber die wirksamen Substanzen des Mutterkorns," *Schweiz. med. Wochschr.*, 2 (1921), 525.

(4) A. Stoll, "Über Mutterkorn," *Schweiz. Apoth.-Ztg.*, Nos. 26–28 (1922).

(5) C. Moir, "Clinical Comparison of Ergotoxine and Ergotamine," *Brit. Med. J.*, 1 (1932), 1022.

(6) C. Moir, "The Action of Ergot Preparations on the Puerperal Uterus," *Ibid.*, 1 (1932), 1119.

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DIGITALIS GLYCOSIDES. E. Leger. (*J. pharm. chim., Paris*, 18 (1933), 482.) This review of the work of many authors upon the digitalis glycosides shows that although these glycosides differ, especially with respect to the number and nature of the sugar molecules with which the aglycones are associated, there is a close relationship between the aglycones themselves. The knowledge of the constitution of one of these aglycones would furnish the key to the constitution of the remainder.—G. M. MELHUISH in *Quarterly Journal of Pharmacy and Pharmacology*, 7 (1934), 127.