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Effect of Tranquilizers on Libido, Sperm Production and *in vitro* Sperm Survival in Dogs.* (28688)

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Tranquilizing drugs, such as chlorpromazine (Thorazine) and promazine (Sparine), have been shown by many workers to inhibit ovulation by interfering with the release of luteinizing hormone (LH). However, Purshottam *et al*(1) have reported that chlorpromazine and promazine inhibit ovulation in mice on a PMS-HCG regimen normally resulting in superovulation; thus, an exogenous source of LH failed to induce ovulation. Barraclough and Sawyer(2) also have demonstrated that chlorpromazine may block the hypothalamic inhibition of luteotropin secretion. Information on the effect of tranquilizers on reproductive function in the male is negligible. Interference with the normal secretion of pituitary gonadotropins in males could occur, but the lack of "ovulatory peaks" may diminish observable effects on gonadotropin inhibition in the male. Gillette (3) and Zimbardo and Barry(4) found that the copulation rate, but not the percentage of rats which would copulate, was reduced by chlorpromazine administration. Direct cellular effects of chlorpromazine and promazine also are known to occur. *In vitro* studies by Foote and Gray(5) indicated that the motility and fertility of bull sperm were unaffected by 200 μg/ml of chlorpromazine, but higher levels of chlorpromazine and promazine were spermicidal. This report is a study of the effect of chlorpromazine and promazine on reproductive function in male dogs.

Materials and methods. Nine mature Beagle dogs weighing from 9 to 11 kg were used. The dogs had been trained for routine semen collection as described by Boucher *et al*(6). Semen samples were collected every third day. The procedure for evaluating, processing and storing the semen in a yolk-citrate-glucose-glycine-antibiotic medium has been described(5,7). The levels of promazine and chlorpromazine tested in the *in vitro* experiments corresponded to levels tested by Foote and Gray(5) with bull sperm. These experiments were completed prior to the time the dogs were administered tranquilizer.

Chlorpromazine was administered orally at the rate of 4.4 mg/kg (2 mg/lb), a dose slightly above the recommended dose given by Scheidy and McNally(8) for sedation. For this phase of the work dogs were paired on the basis of equal sperm output per ejaculate. One member of each of the 4 pairs was randomly assigned to Group A, and the other member to Group B. During period I all dogs were given 5 doses of chlorpromazine

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TABLE I. Motility of Sperm Stored in a Buffered Egg Yolk Medium Containing Promazine and Chlorpromazine.

Exp	Days stored at 5°C	Control, 0 drug	Promazine (μg/ml) 2	20	100	200	2000	Chlorpromazine (μg/ml) 2	20	100	200	2000
			(% motile sperm)									
I (9 ejac)	1	72	71	70	66	—	—	67	70	66	—	—
	4	64	66	63	62	—	—	62	66	65	—	—
	8	52	48	47	45	—	—	49	44	44	—	—
	12	23	23	26	23	—	—	28	24	16	—	—
	Mean	53	52	51	50	—	—	51	51	48	—	—
II (9 ejac)	1	66	—	63	—	63	15	—	63	—	63	44
	4	66	—	61	—	58	3	—	61	—	59	34
	8	62	—	60	—	58	0	—	60	—	47	20
	12	36	—	36	—	28	0	—	38	—	23	1
	Mean	57	—	54	—	51	4	—	56	—	48	25

at 2-day intervals. A 6-day rest interval followed. Then during period II Group A served as a control, receiving no chlorpromazine, and Group B received 9 successive daily doses of 4.4 mg/kg of chlorpromazine.

Results and discussion. Results of 2 experiments with tranquilizing drugs added to the semen of 9 dogs are summarized in Table I. The 2 highest levels of each drug tested depressed sperm motility ($P < .01$). These doses were much higher than those used in *in vivo* studies. None of the lower levels stimulated the motilty of dog sperm, in contrast with the beneficial effects of chlorpromazine on bull sperm previously reported (5).

Administration of 4.4 mg/kg of chlorpromazine produced mild sedation in the dogs. However, when they were brought to the collection area there was no reduction in libido. Dogs mounted the teaser bitch immediately and proceeded rapidly to ejaculate the first fraction of semen. The one extra dog in the group of 9 not assigned to the paired groups was given 8.8 mg/kg. This level of chlorpromazine likewise did not reduce libido.

TABLE II. Sperm per Ejaculate when Semen Was Collected from 4 Pairs of Dogs Receiving Chlorpromazine.

Period	Groups*	Semen collections 1	2	3	4	5	Mean
		(Avg No. of sperm per ejaculate in millions)					
I	A	909	872	818	550	586	747
	B	778	730	892	717	644	752
	Mean	843	802	855	634	615	750
II	A†	601	384	462	452	534	486
	B	613	530	627	559	552	576
	Mean	607	457	544	505	543	531

* Both groups were treated during Period I, but only Group B was treated during Period II.
† Control.

Sperm output (Table II) was not reduced by the treatment; in fact it was actually higher in the treated group in period II ($P = .05$). This may be an aberrant sample, because only 2 of the treated males outproduced their paired controls. Mean sperm output for both groups was similar during period I. Sperm production was unexpectedly high during this period, since previous collections with these dogs averaged 580 million sperm per ejaculate.

Chlorpromazine treatment of the dogs had no effect upon the motility of the sperm collected (Table III). The percentage of motile cells surviving storage in samples collected prior to treatment and during the various intensities of chlorpromazine administration did not differ significantly ($P > .10$).

Thus oral administration of chlorpromazine at levels slightly in excess of those recommended for sedation had no effect on libido. Histological examination of the testes of several dogs following the experiment did not reveal any effect of chlorpromazine upon the interstitial tissue. There was no consistent effect of chlorpromazine upon sperm output or the motility of the sperm collected. Therefore it would appear that 4.4 mg of chlorpromazine per kg of body weight did not alter the normal hypothalamic-pituitary-gonadal relationships in these male dogs. Studies

TABLE III. Motility of Stored Sperm Collected from 8 Dogs Prior to and During Oral Administration of Chlorpromazine.

Period	Days stored at 5°C	Period prior to treatment	Beginning of treatment period			End of treatment period		
			Group A	Group B	Avg of A, B	Group A	Group B	Avg of A, B
			(% motile sperm)					
I*	1	68	70	80	75	75	78	76
	4	65	70	68	69	70	70	70
	8	57	55	55	55	62	68	65
	12	30	38	35	36	40	48	44
	Mean	55	58	59	59	62	66	64
II	1	—	72	78	75	72	75	74
	4	—	68	72	70	70	65	68
	8	—	60	50	55	58	58	58
	12	—	42	35	39	32	38	35
	Mean	—	61	59	60	58	59	58

* See footnote, Table II.

of longer duration and at higher levels of chlorpromazine are necessary before it can be determined whether or not this drug can interfere with reproductive function in the male dog.

Summary. Additions of promazine or chlorpromazine in concentrations below 200 μg/ml of media suitable for prolonged storage of dog sperm were without effect on sperm motility. Higher levels of these drugs were spermicidal. Oral administration of chlorpromazine to 8 dogs (4.4 mg/kg of body weight) every other day or daily for 9 days did not reduce the libido of dogs trained to routine semen collection procedures. Motility of the sperm collected was unaffected, and sperm output was inconsistently higher in the treated group. It is concluded that the *in vivo* levels of chlorpromazine studied did not alter the normal hypothalamic-pituitary-gonadal relationship.

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Lethal Effect of Chlorpromazine on the Chick Embryo.* (28689)

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Chlorpromazine influences a variety of experimental biological systems: it inhibits a number of enzymes and cell respiration, and alters cell and mitochondrial permeability (1-22); it inhibits cell division in fertilized echinoderm eggs and regeneration in planaria and in the axolotl(23); it induces abortion in the mouse and rat, and is a teratological agent in the rat(24-27). The present report describes the lethal effect of this compound on the development of the chick embryo.

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