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The Effects of Gonadal Hormone Manipulations on Aggressive Target-Biting in Mice

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THE EFFECTS OF GONADAL HORMONE MANIPULATIONS ON AGGRESSIVE TARGET-BITING IN MICE

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George C. Wagner

TABLE OF CONTENTS

INTRODUCTION

Most physiological studies of mammalian aggression have shown the androgen, testosterone, to be of critical importance (Beeman, 1947; Leshner, 1975; Leshner & Moyer, 1975; Leshner & Candland, 1973; Leshner, Walker, Johnson, Kelling, Kreisler & Svare, 1973). Testosterone is produced in the interstitial cells of the testes in response to pituitary secretion of luteinizing hormone, LH, and follicle stimulating hormone, FSH (Grumback, 1971). This steroid, in turn, serves as part of a long loop feedback system to inhibit production of hypothalamic releasing factors that control pituitary release of LH and FSH (Cross, 1973). The main target organs of testosterone are the seminal vesicles and prostate but its effect is widespread (Short, 1973). Hypophysectomy or castration will cause atrophy of the seminal vesicles and prostate while testosterone propionate replacement therapy will restore these glands to their normal weights (Bottomley & Folley, 1938). Most physiological responses to testosterone are mediated by binding of the androgen to cytoplasmic constituents of target cells. While the brain is not conventionally viewed as an androgen target organ, autoradiographic studies of the central nervous system have shown androgen uptake is highest in the hypothalamus, septum and amgdyla (Sar & Stumpf, 1973). Electrical stimulation, testosterone implant and lesion studies have shown these areas to be intimately involved in aggressive behavior (Owen, Peters & Bronson, 1974; Slotnick & Mullen, 1972; Hutchinson & Renfrew, 1966; Karli, Vergnes & Didiergeorges, 1969). This suggests that testosterone may play a role in aggression through its effect on the brain.

The study of aggression as a dependent variable is plagued with many problems. A frequently used technique is paired aggressive

fighting in which male mice reared in isolation or hamsters, gerbils and other species, placed in a neutral territory will engage in combative behavior (Banerjee, 1972; Valzilli, 1969; Harding & Leshner, 1971; Wise, 1974; Brain, 1972). Leshner (1975) and Leshner and Candland (1973) have shown that castration will prevent fighting in mice but testosterone propionate replacement will reinstate this behavior. Some species however, (eg. dogs, hamsters, and macaque monkeys) continue to fight after castration (Whitsett, 1975; Moyer, 1974). Also, female mice reared in isolation do not show this response but females masculinized by neonatal testosterone injections will show the aggressive response following another testosterone injection in adulthood. These later findings indicate that after birth there may be a critical time period within which exposure of the central nervous system to androgens is critical for male - like development (Moyer, 1974; Leshner & Johnson, 1974).

In addition to the sex variables and limited choice of species the size of the fight cage as well as its neutrality are important variables in paired fighting tests. Too large a cage yields a marked reduction in fighting and "home" territory correlates highly with fight outcome (Scott, 1966; Anderson & Hill, 1965; Ulrich & Azrin, 1962).

Another very important factor which must be considered when utilizing this measure of aggression is the dominance-submission interaction. Male mice, when reared in a group, do not constantly fight but rather establish a hierarchy. This hierarchy maintains order within the group and, in much the same manner, can be established in paired aggressive fight tests and this in turn affects the test results (Scott, 1966; Lindzy, Winston & Manosevitz, 1961). Therefore, it becomes necessary to make every effort to standardize opponents both within and between experimental investigations.

Another methodology used to study aggression is shock elicited fighting. This technique uses an aversive, environmental stimulus

(electric shock) presented periodically, but simultaneously, to subjects in a confined area (Ulrich & Azrin, 1962). Hutchinson (1973) has shown that these aggressive responses are the result of either antecendent conditions, such as a noxious stimulus or removal of a reinforcing stimulus or consequential conditions such as reinforcement of an attack response or removal of noxious stimuli after attack responses.

Several advantages of this technique are apparent. Many species (rats, cats, mice, monkeys, hamsters, turtles, snakes and others) will respond with attack behavior following shock (Ulrich & Azrin, 1962; Ulrich, Hutchinson & Azrin, 1965). Shock is not the only aversive stimulus capable of eliciting this response. Intense noise and heat will also bring about combative behavior (Ulrich & Azrin, 1962; Hutchinson, 1973). Further, sex and age seem to be less important variables since females will engage in attack responses as well as animals varying widely in age (Hutchinson, Ulrich & Azrin, 1965; Ulrich & Azrin, 1962). This shock elicited paradigm was utilized by Hutchinson et al.(1965) to show that androgen depletion following castration will diminish the attack response.

One important disadvantage of the paired - subject paradigm is that subjective observation is prerequisite for this system, although this is controlled to some extent by the use of two or more trained observers scoring the session. Since it was discovered that animals will reliably attack inanimate objects it has become possible to collect measurements such as latency, frequency and force of attack for various stimuli (Hutchinson & Emely, 1972; Hutchinson, 1973; Hutchinson, Azrin & Hake, 1966; Azrin, Hutchinson & Sallary, 1964; Azrin, Rubin & Hutchinson, 1968). The attack upon inanimate targets is also important since it allows a single subject design and the importance of the dominance-submissive interaction is eliminated. Azrin et al. (1964) and Hutchinson et al. (1966) found that electrical switch closure controlled by the attack

of the inanimate target was a more reliable measure than subjective observation and recording of the attack by humans.

Most aggressive behavior studies have observed aggression as the sole dependent variable. That various procedures are selectively affecting aggression can only be shown by concomitant measures on other dependent variables such as activity levels or learned responses. Brain and Nowell (1969) did find a positive correlation between open field behavior and aggressive scores in mice but no further manipulations were made. However, Eleftheriou, Elias, Cherry and Lucas (1976) found runwheel activity levels and testosterone plasma levels were not related in mice. In general, however, most studies on aggression have ignored the above questions.

The objective of the present study was to manipulate hormone levels via castration and subsequent steroid replacement therapy and observe the effects on both biting attack of an inanimate target, paired fighting and runwheel activity responses. Somatic changes to steroid manipulations were monitored by organ weight measurements. Two experimental phases were used; the first studied male-female differences and basic hormonal manipulations and the second assessed hormonal manipulations as they relate to organ weight, paired fighting observations and runwheel activity.

METHODS

Experimental Animals

Experimental animals were 25 male and 10 female mice of the Upjohn CF - 1 strain (Upjohn Laboratory, Kalamazoo,MI). They were obtained, when seven weeks old, in two experimental phases; the first phase consisted of 10 males and 10 females and the second phase, ordered two months later, consisted of 15 males. They were housed in individual cages with ad libitum access to food and water throughout the experiment. Colony room lights were automatically turned on at 07:00 and off at 22:00.

Apparatus

The test apparatus was a transparent plastic cylinder 9 cm long with a 3.7 cm inner diameter. The tail of the mouse was passed through a slot in the base of the cylinder and affixed with "Dermicel" tape (Johnson & Johnson, New Brunswick, N.J.) to a plastic rod attached parallel to the long axis of the cylinder. The cylinder was then capped with a plastic face and positioned in a larger apparatus which held the bite target and shock electrodes. The target was a stiff nylon strip 0.5 cm wide and between 3.6 and 4.4 cm long. The length of the target varied such that the forward edge reached an imaginary line perpendicular to the long axis of the cylinder and passed just anterior to the eye of the resting animal (Fig. 1). The electrodes were brass bars 0.9 cm wide, 0.9 cm high and 9 cm long. Two such electrodes rested on an untaped portion of the tail although shock was not used in this experiment. The nylon target was connected to a telegraph key. The key, in turn, was wired to electro-mechanical counters and cumlative recorders in a separate room. Biting - tugging actions on the target were thus recorded.

Figure 1. The test apparatus: E = electrodes, PC = plastic cylinder, TK = telegraph key, BT = bite target.

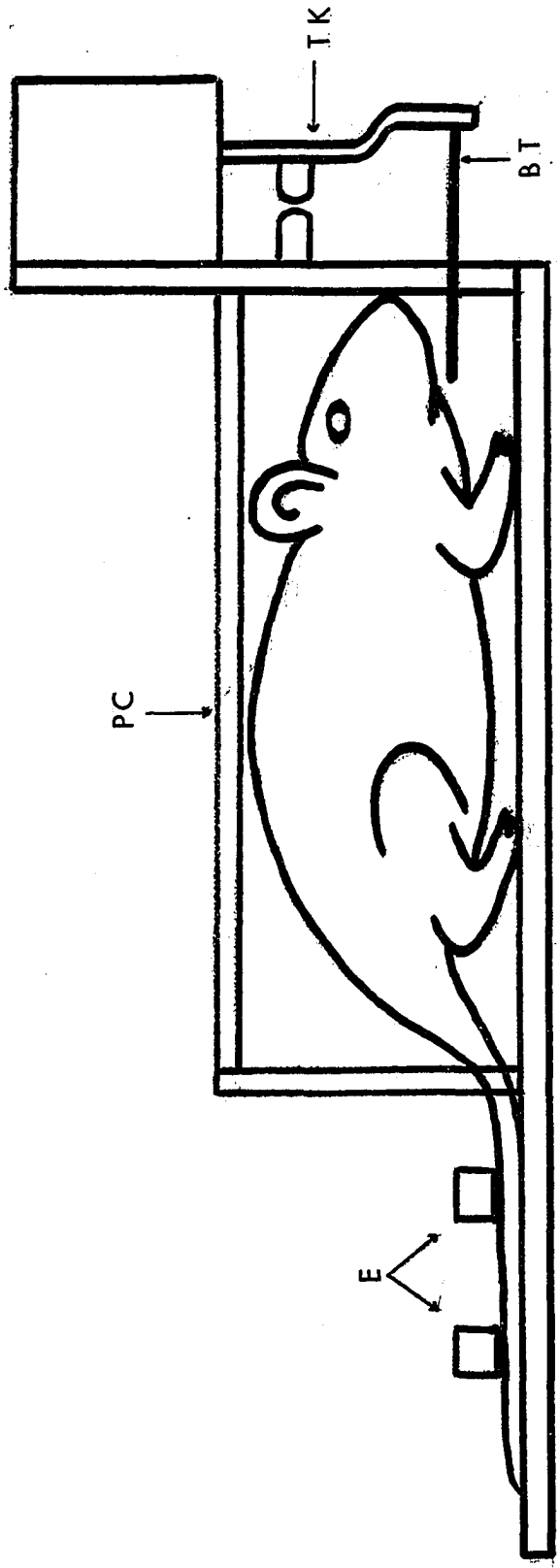


FIG. 1: Test Apparatus

A sound attenuated, temperature and light controlled chamber housed the apparatus. White noise at 60db to mask sounds and air ventilation systems were also used. Four 3 watt bulbs supplied the light from the chamber ceiling.

Procedure

At the same time each morning a mouse was removed from its home cage, placed in the cylinder and its tail was secured to the tail support rod. Body weight was recorded and the cylinder then positioned in the chamber. The test session began with the lights coming on and continued for 15 minutes. The test sessions were conducted on weekdays only.

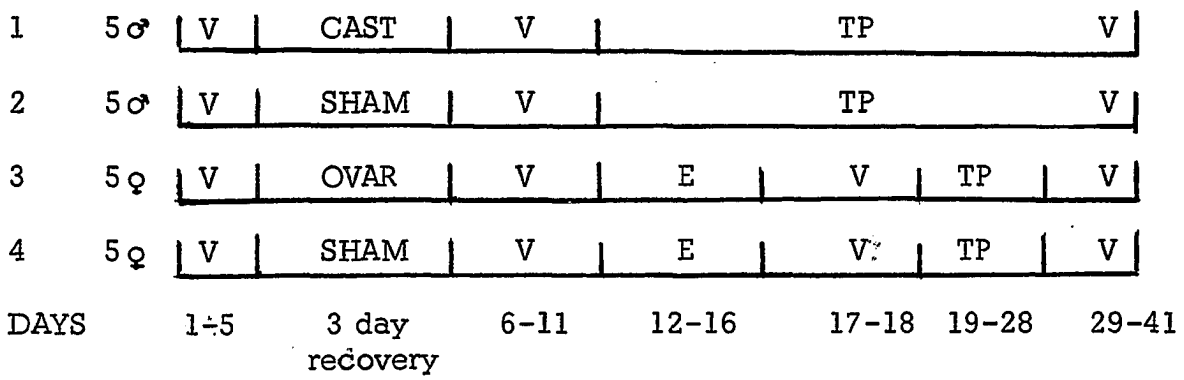
Groups

There was a total of seven groups in the two experimental phases (see Table 1). The first phase had four groups. Group 1 consisted of five males tested first as normals for one week. After each session 0.1 ml of sesame oil was administered subcutaneously. After the first week of testing they were castrated, allowed a three day recovery and then retested for six days. Subcutaneous testosterone propionate (TP) injections (150 μg/day) were then initiated for 26 days on a stepwise gradually reducing dosage regimen until only the vehicle was given (control vehicle injection). Control vehicle injections continued for twelve days.

Group 2 consisted of five males. These mice were treated the same as those of Group 1 for the course of the experiment except that they received only sham operations.

Groups 3 and 4 each consisted of five female mice. These mice were treated the same as those in Groups 1 and 2 with the exception that the animals in Group 3 were ovariectomized and those of Group 4 received sham operations. Estrogen (150 μg/day), however, was

PHASE 1



PHASE 2

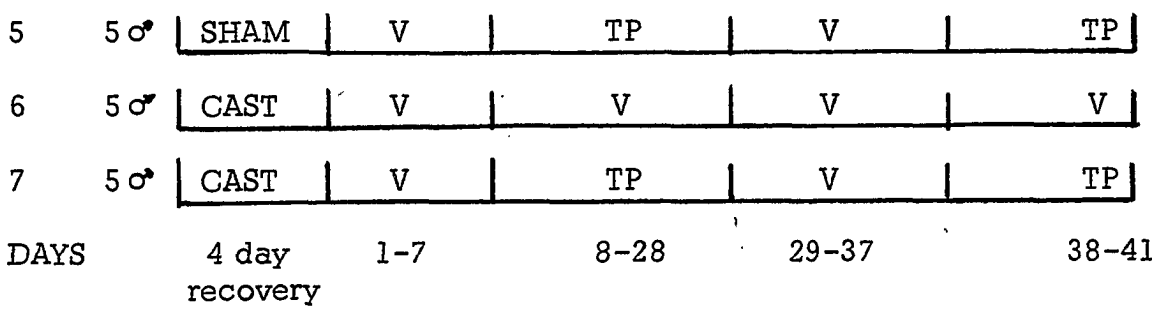


Table 1. Sequence of injections and procedures in days for the seven groups. Numbers below indicate session spans. The two columns of numbers on the left are the group number and number of mice per group, respectively. CAST = castration; OVAR = ovariectomy; V = vehicle injection; TP = testosterone propionate; E = estrogen.

initially given to these females rather than TP. Estrogen injections continued for nine days and were followed by two days of control vehicle injections and then by fifteen days of TP (150 μg/day). Finally, twelve days of control vehicle injections followed the hormone injections. The mice in these first four groups were then sacrificed and seminal vesicle, prostate, uterus and/or adrenal weights were measured.

The second phase consisted of three additional groups containing five males per group. Group 5 animals received a sham operation four days prior to the start of testing. They then were tested for six days with daily control vehicle injections followed by sixteen days of 150 μg/day TP. The dosage was then increased to 250 μg/day for four days and finally five days of control vehicle injections.

The mice of Groups 6 and 7 were treated the same as those of Group 5 except that they were castrated rather than sham operated. In addition, Group 6 mice received only the control injections.

Mice in Groups 5, 6 and 7 were tested for running activity variations. After measurement of biting each day they were placed in a running wheel in an identical chamber for fifteen minutes. The wheel was 15 cm in diameter and 9.9 cm wide. Electromechanical counters recorded the number of revolutions per session.

Finally, one day after the last vehicle injection, Groups 5, 6 and 7 were tested in a standard paired-fighting test paradigm (Edwards, 1970). TP injections were then reinstated for four days at 250 μg/day and the paired fighting test conducted once again. Mice were then sacrificed and seminal vesicle, prostate and adrenal weights were measured.

Nonparametric statistics (Mann - Whitney, with the 2.5% level accepted for significance) were used for tests of significant difference unless otherwise noted.

RESULTS

In phase one, the sham-operated males attacked the bite target significantly more than the sham-operated females during the initial eleven sessions of vehicle only injections. The bites per session means for this comparison were 432 for the males and 31 for the females. This relationship was not altered when TP or estrogen was added to the daily injections over the next seventeen sessions ($\bar{X}$ = 550 & 93 for the males and females, respectively) and persisted when these sham-operated mice received vehicle only injections over the last fifteen sessions ($\bar{X}$ = 497 & 84; see Fig. 2).

The bites per session means for the 150 µg/day, 75 µg/day and 30 µg/day TP injections for the sham-operated males were 542, 543 and 573. No statistical comparison between these three treatments themselves and the predrug and postdrug vehicle only treatments showed statistical differences (see Fig. 2C).

The means for the vehicle only and 150 µg/day estrogen treatments in the sham-operated females were a nonsignificantly different 31 and 26 respectively. When TP was administered to these females the mean number of bites per session significantly increased to 123 for the twelve day period (see Fig. 2D).

When normal males were castrated the bite attack level dropped significantly from a preoperative level of 635 to a postoperative level of 87. Overiectomizing the normal females did not significantly alter their bite attack levels ($\bar{X}$ = 75 preoperative and 47 postoperative, see Fig. 2A and B).

The 150 µg/day, 75 µg/day and 30 µg/day TP injections increased the bite attack means of the castrated males to 421, 534 and 425, respectively. Each of these treatment increases was significantly

Figure 2. Plot of biting attack means over sessions for phase one mice. Treatments are indicated above graphs. TP = testosterone propionate, V = control vehicle injections, E = estrogen, cast = castration, ovar = ovarectomy. ■-■ = normal male; □---□ = cast male; O-O = normal female; △---△ = ovar female.

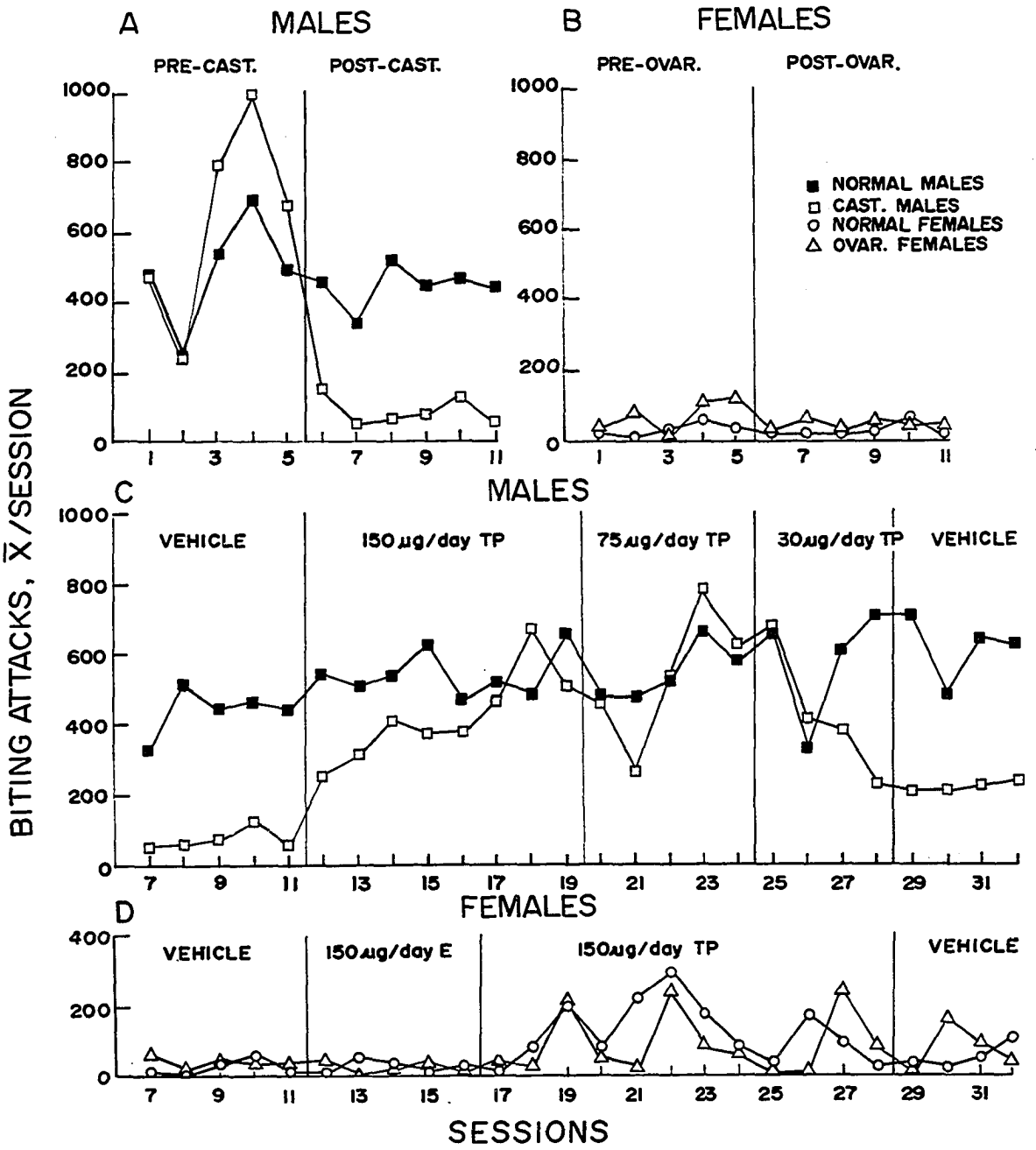


FIGURE 2

greater than the predrug bite attack levels. Estrogen administered to the ovarectomized females had no effect on the bite attack response but when TP was administered the mean increased to 91 although this difference was not significant when compared with predrug bite attack levels (see Fig. 2C).

Figure 3 presents the dose response curve for the castrated males and their TP injections. Bites per session calculations were based only on the last three days for each treatment dosage to eliminate any possible influence from the previous treatment. It is apparent that the greater the dosage the higher the bite attack frequency. At 75 μg/day there seems to be a maximal effect since doubling the dosage did not alter the bite attack level.

Table 2 is an organ weight table depicting results of surgical manipulations. For males, the seminal vesicle and prostate weights were significantly greater in the sham operated groups than in the castrated groups and for the females, there was a significant difference between uterus weights of sham operated and castrated groups with the sham operated group having the heavier uterus.

In phase two, sham operated males attacked the bite target significantly more than castrated males ($\bar{X}$ = 298 & 59, respectively). When TP was administered to one group of castrated males, attack levels were increased significantly ($\bar{X}$ = 181) as compared to control castrated males ($\bar{X}$ = 48). The bite attack frequencies for the sham operated males did not show a significant difference between the predrug mean ($\bar{X}$ = 298) and the 150 μg/day TP treatment mean ($\bar{X}$ = 279). Increasing the dosage to 250 μg/day had no significant effect on either the sham operated males ($\bar{X}$ = 235) nor the castrated, TP treated males ($\bar{X}$ = 188). When TP injections were discontinued the mean bite attack frequency of castrated males decreased significantly to 86 while the sham operated males attack level increased only slightly to 307 (see Fig. 4A).

		Body wt. (g)	Adrenal gland wt. (mg)	Seminal vesicle wt. (mg)	Prostate wt. (mg)
Control Males	$\bar{X}$	42	1.3	6.2	15.8
	R	39-48	1.0-1.5	4.6-8.0	12.8-20.7
Cast. Males	$\bar{X}$	39	1.7	3.0	8.9
	R	36-41	1.1-2.3	2.4-4.3	2.7-11.2

				Uterus
Control Females	$\bar{X}$	34	1.6	3.6
	R	31-36	1.1-2.6	2.7-4.9
Ovar. Females	$\bar{X}$	39	1.6	1.8
	R	33-42	1.3-2.4	1.6-2.2

Table 2. Phase one body and organ weights measured twelve days after the last TP injection. $\bar{X}$ = mean; R = range

Figure 3. Dose-response curve for phase 1, castrated males.

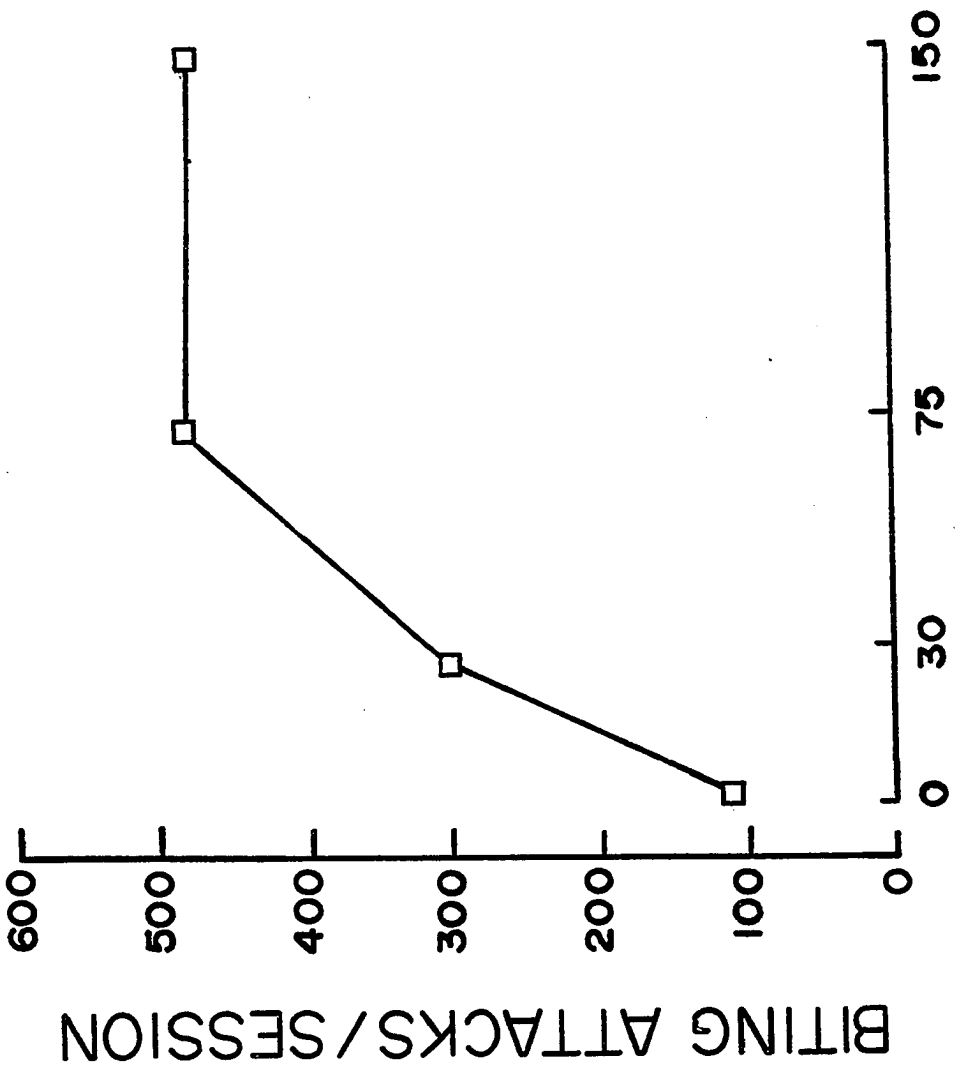


FIGURE 3

	PRE TP				POST TP			
	FIGHTS		LATENCY		FIGHTS		LATENCY	
S	#1	#2	#1	#2	#1	#2	#1	#2
21	54	54	153	153	55	52	10	11
22	65	67	154	154	128	124	7	10
23	86	88	4	4	69	60	6	7
24	81	70	10	10	97	92	7	10
25	109	109	13	14	96	80	5	5
GROUP 5								
26	28	24	52	53	0	0	300	300
27	8	5	160	162	0	0	300	300
28	3	2	264	264	41	45	169	168
29	19	23	157	157	0	0	300	300
30	43	48	9	10	41	45	169	168
GROUP 6								
31	0	0	300	300	50	50	150	151
32	19	12	242	244	63	59	126	126
33	40	40	105	108	8	9	258	259
34	21	19	163	164	87	87	1	2
35	0	0	300	300	35	32	233	234
GROUP 7								

Table 3. Paired aggressive fight and latency scores for each of the fifteen mice (S) in phase two. The scores are presented for both observers (#1 & #2). Latency scores are in seconds. A fight response was scored if either mouse lunged at its oponent in a biting attempt.

Runwheel activity levels were not affected significantly by any surgical or hormonal treatment. There was, however, an increasing trend in runwheel performance since there was a significant increase in total revolutions for all groups combined when the first five sessions are compared with the last five ($\bar{X}$ = 205 & 348; see Fig. 4B).

The data from the paired fighting test are summarized in Table 3. The correlation between total paired fights and total bite attacks was .79 which was significant to $p < .01$ (see Fig. 5).

Table 4 presents organ weights for the three groups of phase two. The TP treatment was sufficient to significantly increase both seminal vesicle and prostate weight in the drug treated group of castrates as compared with castrates treated with the vehicle.

		Body wt. (g)	Adrenal wt. (mg)	Seminal vesicle wt. (mg)	Prostate wt. (mg)
Control Males & TP	$\bar{X}$	45	1.0	9.2	19.0
	R	42-48	.77-1.2	7.2-13.9	17.1-21.0
Cast. Males & TP	$\bar{X}$	43	1.1	3.9	13.2
	R	39-50	1.0-1.4	2.4-5.7	10.4-16.3
Cast. Males & V	$\bar{X}$	42	1.2	1.6	8.8
	R	38-42	.88-1.9	.83-2.7	5.3-11.0

Table 4. Body and organ weight measurements of phase two measured one day after the last TP injection. $\bar{X}$ = mean; R = range

Figure 4. Plot of biting attack mean and running revolution over sessions for phase two. Treatments are indicated above graphs. ■-■ = normal male; O-O = cast male treated with TP; Δ---Δ = cast male, no TP treatment.

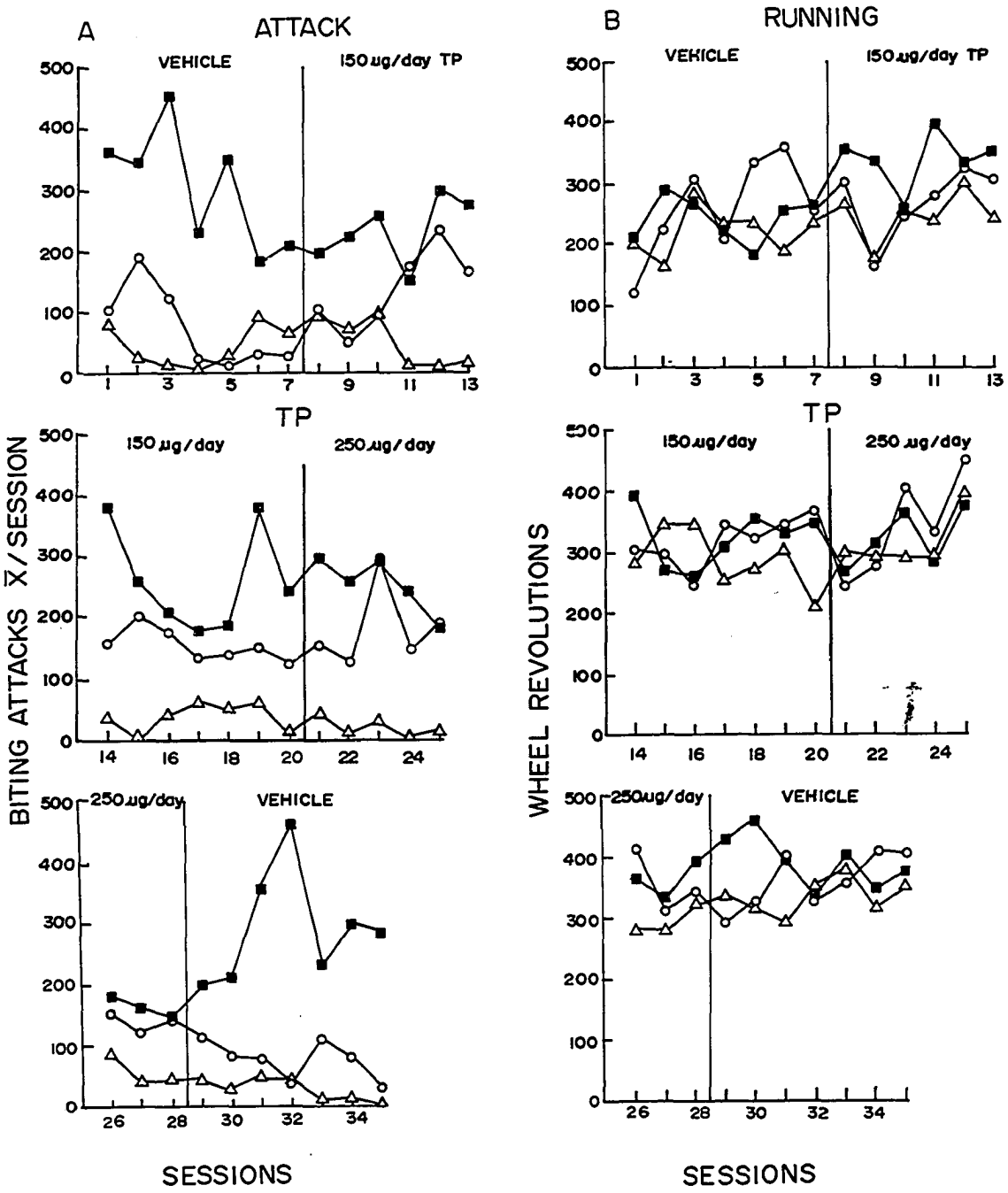


FIGURE 4

Figure 5. Plot of biting attack means for the last five TP sessions vs. paired fighting "fight" scores. Fight scores for both the pre and post TP tests (Table 3) were combined for this figure. ■-■ = normal male; O-O = cast male treated with TP; Δ---Δ = cast male no TP treatment.

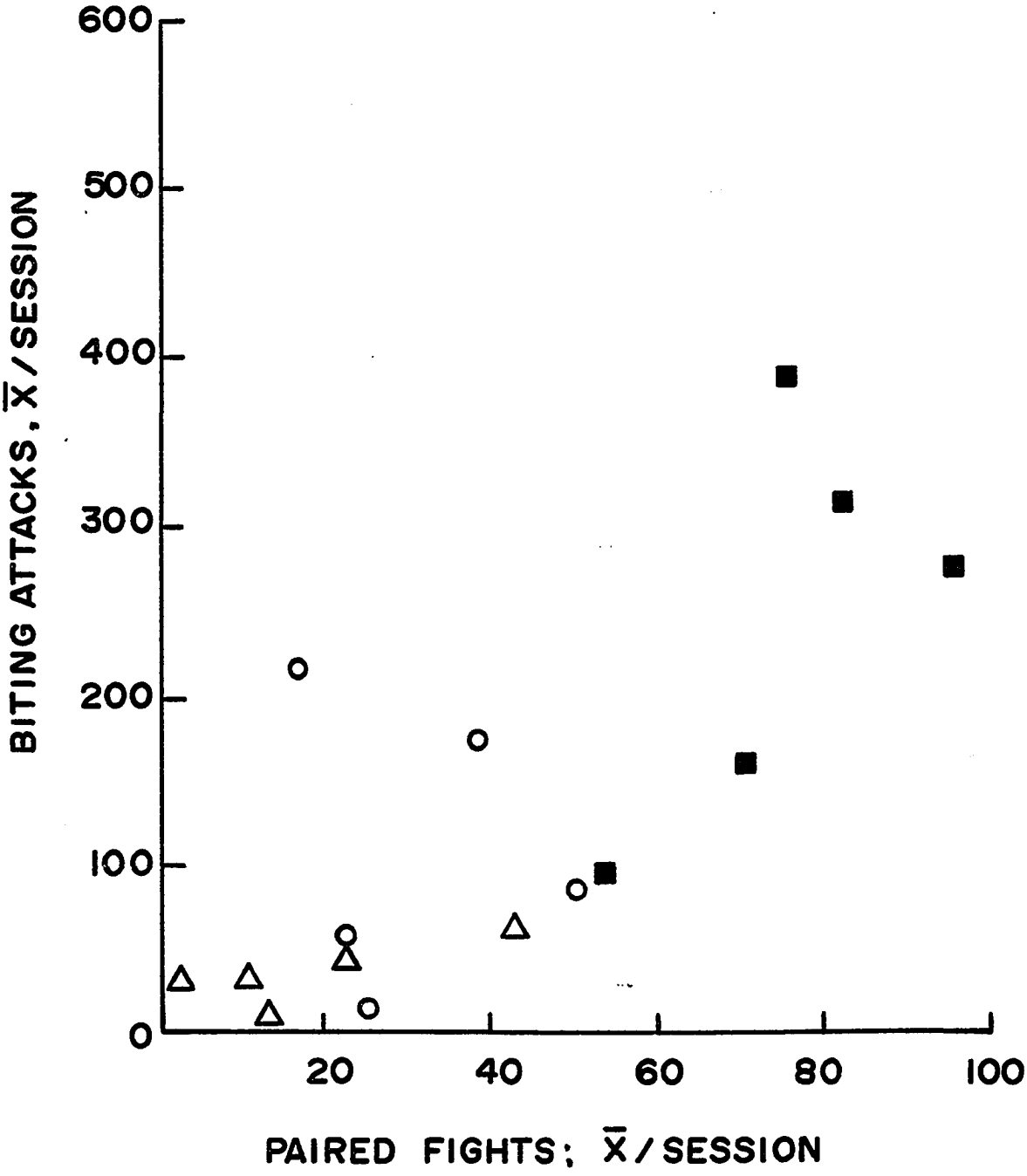


FIGURE 5

DISCUSSION

The present test paradigm proved very effective as a means for studying aggressive behavior. No additional stimulus, such as electric shock, was necessary to bring out biting behavior; the restraint of the test apparatus alone was sufficient. The advantages of a simple system consisting of chamber, target and counter make this system highly conducive as a potential means of generating quick, inexpensive but reliable measurements on effects of pharmacological agents. The additional advantages of single subject design, eliminating dominance-submissive interactions as well as injury to the target animal are also important.

The high correlation with the more standard paired-fighting aggression test and the fact that bite attack levels were manipulated by castration and TP injections without affecting the runwheel activity levels indicates this new test design is one of importance for future research in the pharmacological and physiological study of aggression. The high correlation of the TP on organ weight, biting frequency and paired fighting was indicative of the sensitivity of this test.

The finding of the differences between male and female groups of mice might be expected considering the literature indicates that the male is more aggressive than the female (Beeman, 1947; Brain, 1972; Leshner, 1975). This study presents this finding in a more objective manner with a direct comparison of bite attack frequencies of male and female mice. Both untreated controls and TP treated males had higher levels on this response than the control or TP or estrogen treated females.

The additional finding that castrated males were less aggressive than normal males was also to be expected on the basis of the experiments cited above. The fact that TP injections increased the bite attack levels

of the castrated males was also expected considering the conclusive evidence that TP restores aggressive behavior to castrated males in the paired-fight test model. That this TP effect is not a generalized stimulant effect is indicated by the lack of any change in the runwheel activity levels taken during phase two. However, the increase noted in the normal females with the TP treatment was not expected since previous literature indicated that a neonatal injection was prerequisite for such an androgen effect, at least in the paired fighting tests. Further studies are needed to clarify the role of androgens in female aggression. Estrogens were not effective in increasing the aggressive activity of the females but perhaps pregnancy and the gamet of hormonal changes associated with it would do so. Moyer (1974) has indicated that pregnancy markedly increases the aggressiveness of mice.

The dose response curve of phase one is interesting in two respects. First, there is a maximal effect at 75 μg TP/day beyond which higher dosages seem to have little additional effect on increasing the bite attack levels. This aspect is further indicated by the fact that TP given to males with intact testes also did not further increase their aggressive response. This later finding, however, may be related to the fact that exogenous testosterone inhibited pituitary LH secretions and consequently there was no change in circulating testosterone levels. Second, it can be seen from the dose response curve (Fig. 3) that within limits, there is a monotonic relationship between testosterone replacement and the bite attack level.

Finally, the TP was sufficient to restore the atrophied testosterone target organs (Tables 2 and 4), to increase paired fighting in the castrated males (Table 3), and to increase the bite attack response in the castrated males but not the intact males. In addition, TP had no effect on the runwheel activity levels. This study, therefore confirms and extends

(and objectifies) the literature indicating the importance of androgens in the regulation of aggression.

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