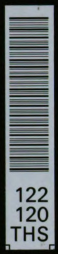

THESIS

This is to certify that the

thesis entitled

Male Sexual Behavior in Deermice
(Peromyscus Maniculatus) Following
Castration and Hormone Replacement

presented by

Steven M. Pomerantz

has been accepted towards fulfillment
of the requirements for

M.A. degree in Psychology

Major professor

Date 11-5-80

O-7639

MALE SEXUAL BEHAVIOR IN DEERMICE (*PEROMYSCUS MANICULATUS*) FOLLOWING CASTRATION AND HORMONE REPLACEMENT

By

Steven M. Pomerantz

A THESIS

Submitted to
Michigan State University
in partial fulfillment of the requirements
for the degree of

MASTER OF ARTS
Department of Psychology
1980

ABSTRACT

MALE SEXUAL BEHAVIOR IN DEERMICE
(PEROMYSCUS MANICULATUS) FOLLOWING
CASTRATION AND HORMONE REPLACEMENT

By

Steven M. Pomerantz

The present study investigated the role of gonadal hormones in mediating male copulatory behavior in male deermice (Peromyscus maniculatus). Sexually experienced male deermice were castrated and tested for male sexual behavior. In the weeks following castration male sexual behavior decreased. Ejaculation disappeared first, followed by intromission and, finally, mounting. Castrated males who no longer copulated were assigned to one of four treatment groups: 200 ug testosterone propionate (TP); 200 ug dihydrotestosterone propionate (DHTP); 2 ug estradiol benzoate (EB); or sesame oil (OIL). TP and DHTP were both effective in restoring the complete male sexual behavior pattern. In contrast, EB was effective in inducing mounting and minimally effective in inducing intromissions (vaginal penetration), but did not induce any ejaculatory responses. These data indicate that in deermice there is a greater likelihood that testosterone may mediate male sexual behavior through reduction to dihydrotestosterone than through aromatization to estradiol.

ACKNOWLEDGEMENTS

I offer many thanks to Dr. Lynwood G. Clemens for his enthusiastic support and advice during this research project. I also wish to thank Dr. Lauren J. Harris, Dr. John I. Johnson, Jr., and Dr. John A. King for their thoughtful comments and suggestions.

I also acknowledge the helpful editorial assistance made by Gary Dohanich, Steven Gitterman, and Nancy Secor in preparing this manuscript.

Finally, I affectionately recognize my parents for their encouragement of my academic ambitions.

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INTRODUCTION

Male sexual behavior is influenced by the endogenous secretion of testicular hormones. Traditionally, a basic methodological approach has been employed when characterizing the role of gonadal hormones in mediating male copulatory behavior. The first step involves removing the testes and observing the effects on the physiology and behavior of the animal. The next step is to attempt to counteract the effects of castration through the administration of appropriate gonadal hormones. Finally, the last and most difficult step is to determine the sites and mechanism of action by which testicular hormones are having their facilitative effects.

Effects of Castration

Castration of males in all mammalian species that have been studied results in a decreased frequency of copulatory behavior; however, the rate and degree to which specific components (i.e. mounting, intromission and ejaculation) of the sexual response decline varies among different species. In some species following gonadectomy the intromission and ejaculation responses are lost simultaneously, while in others intromission is maintained for some time after the animal is no longer ejaculating. In all species that have been studied mounting responses and other precopulatory behaviors (i.e. anogenital sniffing, touching,

vocalizing, etc.) are the last components of the male sexual response to decline (reviewed in Larsson, 1979).

In addition to castration resulting in deterioration or disappearance of male sexual activity, investigators have also noted other effects on the mating performance of males continuing to copulate. In castrated male rats gonadectomy produced an increase over preoperative levels in time to first intromission (intromission latency) and time from first intromission to ejaculation (ejaculation latency) (Davidson, 1966). Fewer intromissions were required for ejaculation (Davidson, 1966). Also, in both rats and hamsters the frequency of mounting (without vaginal insertion) increased for a short time following gonadectomy (Beach and Pauker, 1949; Davidson, 1966).

Several morphological changes in the penis of the castrated male parallel his decline in sexual responsiveness. There is a decrease in weight and size of the glans and, also a decrease in number of epithelial papillae "penile spines" (Feder, 1971; Phoenix, Copenhaver, and Brenner, 1976). Whether these morphological changes cause functional disturbances in sexual behavior is not known. However, peripheral atrophy appears to be related to the deficits seen in copulatory performance (increase in mounts without intromission).

Restorative Effects of Testosterone

In all species that have been studied, male sexual behavior of castrated males can be restored by testosterone (T) treatment in a dose dependent manner (guinea pig, Grunt and Young, 1953; rat, Beach and

Holtz-Tucker, 1949; Larsson, 1966; hamster, Tiefer and Johnson, 1973; albino mouse, Luttge and Hall, 1973; Champlin, Blight, and McGill, 1963; rabbit, Beyer and Rivaud, 1973; red deer, Lincoln, Guiness, and Short, 1972; rhesus monkey, Phoenix, Slob, and Goy, 1973). It has generally been reported that rehabilitative effects of T on copulatory behavior begin to appear after several days of treatment. Mounting behavior returns before intromission and ejaculation. However, in some long-term castrated rats mounting and intromission were restored 24 hr after initial T treatment (Beyer, Morali, Naftolin, Larsson, and Perez-Palacios, 1976) and penile reflexes were restored within 8 hr after initial T treatment (Hart, 1980).

Many studies have investigated whether T can restore sexual behavior of castrated males to intact levels. In mice (Champlin et al., 1963), guinea pigs (Grunt and Young, 1952; 1953) and hamsters (Beach and Pauker, 1949; Tiefer and Johnson, 1973; Whalen and DeBold, 1974) the mating performance of castrated males receiving T was no different from intact males. In rhesus monkeys and rats differences in mating performance between intact and T-treated castrated males have not consistently been reported. Some studies report deficits in the T-treated castrates (Beach, 1944; Beach and Holtz-Tucker, 1949; Larsson, 1966; Michael and Wilson, 1974), whereas others report a complete restoration of sexual behavior to preoperative levels (Feder, 1971; Phoenix et al., 1973; Whalen and Luttge, 1971).

Biochemistry of Testosterone Metabolism

It has been demonstrated in a number of mammalian species with both in vivo and in vitro studies that cells in the central nervous system and genital tissues possess specific enzymes which metabolize T to various other steroid hormones. Specifically two major metabolic pathways are: (1) metabolism by aromatase enzymes (aromatization) resulting in the production of estrogen (Callard, Petro, and Ryan, 1978; Dorfman and Ungar, 1965; Flores, Naftolin, and Ryan, 1973, Lieberburg and McEwen, 1975; Naftolin, Ryan, Davies, Reddy, Flores, Petro, Kuhn, White, Takooda, and Wolin, 1975; Weisz and Gibbs, 1974) and (2) metabolism by 5α-reductase enzymes (5α-reduction) leading to the production of dihydrotestosterone (DHT) and other 5α-reduced androgens (Bruchovsky and Wilson, 1968; Jaffe, 1969; Massa, Justo, and Martini, 1975; Sholiton, Taylor and Lewis, 1974; Sholl, Robinson, and Goy, 1975; Whalen and Rezek, 1972). Currently, it is believed that in mammals DHT is incapable of being converted to E and vice versa.

The potential importance of CNS metabolism of T is underscored by reports that the extent of aromatization and 5α-reduction varies among different discrete hypothalamic and limbic brain regions (Selmanoff, Brodkin, Weiner, and Siiteri, 1977; Sheridan, 1979). Furthermore, in these same anatomical locations biochemical and autoradiographic studies have revealed the existence of specific E and DHT binding macromolecules, hypothesized receptor sites (Kato and Onouchi,1975; Lieberburg and McEwen, 1977; Pfaff and Keiner, 1973; Sar and Stumpf, 1977; Zigmond and McEwen, 1970).

Effects of Dihydrotestosterone in the Male Rat

Reports that DHT is more potent than T in promoting cell proliferation and growth of genital tissues (Dorfman and Shipley, 1956; Luttge and Whalen, 1970) have led to the currently accepted notion that T exerts its stimulatory action on peripheral reproductive tissues through its intracellular 5α-reduction to DHT (Bruchovsky and Wilson, 1968; Gloyna and Wilson, 1969; Mainwaring, 1975). Recent support for this hypothesis was reported in CD-1 mice in which in vivo inhibition of 5 -reductase activity with the compound 4-androsten-3-one-17 -carboxylic acid (17 C) effectively blocked the stimulatory effects of T on seminal vesicle and penis growth, but did not interfere with DHT-stimulated growth of these tissues (Luttge, Jasper, Gray, and Sheets, 1977).

Since DHT is considered to be the active metabolite of T in peripheral sex tissues, a logical extension of this concept was to determine whether DHT was also the active metabolite of T in CNS structures mediating male sexual behavior. McDonald and co-workers (1970) reported that DHT propionate (DHTP) administered at a dosage of 125 ug/day for 8 days to sexually inexperienced rats that had been castrated six weeks previously failed to induce copulatory behavior. Males given similar treatment with testosterone propionate (TP) exhibited copulatory behavior equivalent to intact controls. Many other studies have replicated this finding for DHT and other 5α-reduced androgens (Beyer, Larsson, Perez-Palacios, and Morali, 1973; Feder, 1971; Feder, Naftolin, and Ryan, 1974; Johnston, Grunwell, Benson, Kandel, and Petro, 1975; Larsson, Sodersten, and Beyer, 1973; Larsson, Sodersten, Beyer, Morali,

and Perez-Palacios, 1976; Luttge, Hall, Wallis, and Campbell,1975) but have gone further in showing that the castrates could not maintain sexual behavior when hormone replacement was initiated immediately following castration (Parrott, 1974, 1976; Whalen and Luttge, 1971; Yahr and Gehrling, 1978).

In contrast to these findings several studies reported that under certain conditions DHT can stimulate sexual behavior in some castrated male rats. Although not so effective as T, DHT implanted into the preoptic area of the brain did activate male sexual behavior in some long-term castrated males (Johnston and Davidson, 1972). Whalen and Luttge (1971) found that when DHT (800 ug/day) was administered immediately following castration it was not effective in maintaining sexual behavior, but when administered to long-term castrated males, DHT was effective in restoring male copulation. Similarly, in two other studies ejaculatory responses were restored in at least 50% of long-term castrated males receiving either 500 ug or 1 mg daily DHT treatment (Paup, Mennin, and Gorski, 1975; Sodersten, 1975) and 33% of long-term castrates receiving 200 ug/day DHTP treatment (Baum and Vreeburg, 1976). Several points are noteworthy in reviewing these studies. First, in maintenance paradigms DHT(P) has always been found to be ineffective in promoting male sexual behavior. By contrast, in reinstatement paradigms, DHT(P), when administered at a sufficiently high dosage over an extended period of time, was quite effective, although not as potent as T, in restoring the complete male copulatory pattern. DHT also has been found to be more potent in the free alcohol state than in its esterified state (DHTP). Thus, it appears that DHT is not the major

active metabolite of T mediating male sexual behavior in the rat. However, DHT can exert a stimulatory action in the CNS and periphery which facilitates male sexual behavior and growth of genital tissues.

Importance of Aromatization of Androgens in the Male Rat

Until recently, as a result of the large number of studies finding that 5α-reduced androgens failed to promote male copulatory behavior in the rat, the focus of research has been on determining whether or not aromatization of androgens to estrogen was necessary for an androgen to centrally mediate male sexual behavior (McDonald et al., 1970). This hypothesis was supported by findings that T, other aromatizable androgens and E were effective in fully stimulating male sexual behavior in castrated rats (Ball, 1937, 1939; Beach, 1942; Beyer et al., 1973; Davidson, 1969; Johnston et al., 1975; Morali, Larsson, Perez-Palacios, and Beyer, 1974; Parrott, 1974, 1975, 1976, Sodersten, 1973; Whalen and Luttge, 1971).

A more definitive test of whether T must be aromatized to E for the induction of male copulation in the rat was provided by experiments which blocked either the aromatization of T to E or the E receptor itself. Christensen and Clemens (1975) demonstrated that intrapreoptic administration of the aromatization inhibitor, 1,4,6-androstatriene-3,17-dione (ATD), blocked T-stimulated male sexual behavior in castrated male rats. However, sexual behavior was restored in male rats receiving intrapreoptic administration of E alone or in combination with ATD. Similarly, other reports indicated that mating behavior is inhibited in

castrated male rats receiving systemic injections of both T and an aromatization blocker, but males treated with E and DHT in addition to the aromatization blocker exhibited normal copulatory behavior (Beyer et al., 1976; Morali, Larsson, and Beyer, 1977). Further support for the aromatization hypothesis came from studies finding that administering compounds which block the E receptor inhibited T-stimulated male sexual behavior (Luttge, 1975; Beyer et al., 1976).

Although it might be concluded from these studies that male sexual behavior can be accounted for solely by the action of estrogenic metabolites of T, other evidence questions the validity of this conclusion. For example, systemic treatment with E stimulated the full copulatory pattern only when administered at extremely high dosages and over a long period of time (Davidson, 1969; Sodersten, 1973). Moreover, adrenalectomy blocked ejaculations in E-treated rats; therefore, suggesting the possibility that androgens of adrenal origin may be partially responsible for the facilitative effects of E on copulation (Gorzalka, Rezek, and Whalen, 1975).

Combined Action of Estrogen and Dihydrotestosterone in the Male Rat

Recent studies have addressed the possibility that E may stimulate male mating behavior by acting synergistically with either peripherally- or intracerebrally-acting androgens. Castrated male rats exhibited mounting, intromission and ejaculation following treatment with subthreshold dosages of E plus DHT (Baum and Vreeburg, 1973; Feder et al., 1974; Larsson et al., 1973). Neither of these hormones when given alone

stimulated intromission or ejaculation, but some of the E-treated males exhibited mounting. In addition, Davis and Barfield (1979) reported that a higher percentage of castrated male rats administered E in the medial anterior hypothalamic-preoptic area in conjunction with systemically administered DHT exhibited the full copulatory pattern than males receiving intracerebral E or DHT treatment alone. On the basis of these studies it was proposed that the neural mechanisms controlling copulatory behavior are mediated by the estrogenic metabolites of T, whereas 5α-reduced metabolites of T facilitate sensory inputs important for copulation by acting peripherally to stimulate the sex organs. This concept of a non-neural site of action for DHT was challenged in a study by Lodder and Baum (1977). Penile factors contributing to sexual performance were reduced or eliminated by bilaterally transecting the pudendal nerve. This operation, in addition to reducing the occurrence of penile erections, eliminated intromissions and ejaculations. However, pudendectomized and castrated males given DHT + E had a higher mounting frequency than males given TP or E alone. It was suggested from these data that both DHT and E act synergistically in the CNS to control male copulation.

The spinal cord appears to be one likely site of action for DHT. Radioactive labelled DHT, but not E, has been shown to accumulate in ventral horn motor neuron nuclei in the lumbar spinal cord (Breedlove and Arnold, 1979; Sar and Stumpf, 1977b). This finding correlates well with reports that either DHTP or TP, but not E, activated sexual reflexes in spinally transected castrated male rats (Hart, 1979). These

results further supported the hypothesis that both aromatized and 5α-reduced metabolites of T have important CNS effects mediating male copulatory behavior in the rat.

Comparative Studies of Hormonal Mediation of Male Sexual Behavior

Other mammalian species have not been so extensively studied as the rat; however, evidence has accumulated concerning the role played by T's metabolites in activating male sexual behavior. Table 1 provides a brief review of the studies carried out to date. DHT(P) was effective in stimulating copulation in rabbits (Agmo and Sodersten, 1975; Beyer and Rivaud, 1973), hamsters (DeBold and Clemens, 1978; Whalen and DeBold, 1974), Swiss Webster mice (Luttge and Hall, 1973), CD-1 mice in maintenance paradigms only (Wallis and Luttge, 1975), guinea pigs (Alsum and Goy, 1974) and rhesus monkeys (Phoenix, 1974), but was ineffective in sheep (Parrott, 1978). In addition to rats, E promoted copulatory behavior in CD-1 mice (Wallis and Luttge, 1975), Swiss Webster mice (Edwards and Burge, 1971), red deer (Fletcher, 1978), hamsters (DeBold and Clemens, 1978; Noble and Alsum, 1975) and sheep (Parrott, 1978), but was without effect in rabbits (Beyer, de la Torre, Larsson, and Perez-Palacios, 1975), guinea pigs (Alsum and Goy, 1974) and rhesus monkeys Phoenix, 1978). In rabbits (Agmo and Sodersten, 1975), sheep (D'Occhio and Brooks, 1976), hamsters (DeBold and Clemens, 1978) and CD-1 mice (Wallis and Luttge, 1975) synergistic actions of E and DHT have been reported.

Table 1. Hormonal Mediation Of Male Sexual Behavior In Mammalian Species Other Than Rattus Norvegicus

Species	Conclusions
Guinea Pig (Cavia porcellus)	DHTP was as effective as TP in restoring sexual behavior. EB has no restorative effects (Alsum and Goy, 1974).
Hamster (Mesocricetus auratus)	DHTP activated complete copulatory pattern, but was less effective than TP over long-term administration. EB restored mounting behavior, but not intromission or ejaculation. Best results produced with EB acting synergistically with DHT (Christensen et al., 1973; DeBold and Clemens, 1978; Noble and Alsum, 1975; Payne and Bennet, 1976; Whalen and DeBold, 1974).

Table 1 (Cont)

Species	Conclusions
Albino Mouse (*Mus musculus*)	(1) CD-1 strain: EB maintained and restored copulatory behavior, but was less effective than TP. DHT was less potent than EB in maintaining sex behavior and was unable to restore copulation in long-term castrated males. EB + DHT more potent than EB or DHT alone (Luttge and Hall, 1973; Wallis and Luttge, 1975). (2) Swiss Webster: DHT was as potent as TP in stimulating the complete copulatory pattern. EB restored mounting behavior only (Edwards and Burge, 1971; Luttge et al., 1974).
Rabbit (*Orycytolagus cuniculus*)	DHT was less potent than T in activating copulation. EB has no stimulative effects. Best results produced with EB acting synergistically with DHT (Agmo and Sodersten, 1975; Beyer and Rivaud, 1973; Beyer et al., 1975).

Table 1 (cont)

Species	Conclusions
Red Deer (*Cervus elaphus*)	EB was more potent than TP in maintaining copulatory behavior. DHT not tested (Fletcher, 1978).
Rhesus Monkey (*Macaca mulatta*)	DHTP restored complete mating pattern, but was less potent than TP. EB has no restorative effects. 19-hydroxytestosterone (aromatizable androgen) did not induce copulation (Phoenix, 1974, 1976).
Sheep (*Ovis aries*)	EB was less effective than TP in activating sexual behavior. DHT has no stimulative effects. DHT + EB more potent than EB alone (D'Occhio and Brooks, 1976; Parrott, 1978).

Among the many different species of muroid rodents research concerned with hormonal determinants of male copulatory behavior has been conducted exclusively on the laboratory rat (Rattus norvegicus), laboratory mouse (Mus musculus) and golden hamster (Mesocricetus auratus). This lack of diversity points to a need to extend the number of species being studied so that general principles of hormonal factors regulating male sexual behavior can be derived.

Dewsbury (1979) has recently reported normative data on male copulatory behavior in deermice (Peromyscus maniculatus bairdi). The present study sought to characterize the role played by gonadal hormones in mediating male reproductive behavior in this cricetid species. Specifically, the pattern of decline of male mating behavior and performance was examined following castration. Secondly, in castrated male deermice T, DHT, and E were compared for their effectiveness in stimulating male copulation. All results were discussed in relationship to similar experiments performed using other mammalian species. In this manner the comparative base for understanding hormone-behavior interactions could be further expanded.

EXPERIMENT 1

The purpose of this experiment was to assess the effects of castration on male sexual behavior in P.m. bairdi.

METHOD

Subjects.

The subjects in this experiment were 45 male P.m. bairdi bred in the laboratory from stock originally trapped in East Lansing, Michigan. All were at least 120 days old at the beginning of behavioral testing. Males were selected on the basis of having achieved two ejaculations within a test on at least two out of three copulatory behavior tests, one of which being their third behavioral test. Precastration data were collected from these selection tests. Once the ejaculation criterion was achieved the males were castrated under Metofane (Pitman-Moore, Inc.) anesthesia and housed individually in plastic cages, 48 X 27 X 13 cm. Wood shavings were used for bedding and cotton Nestlets (Ancare Corp.) were provided as nesting material. Deermice were maintained on a reverse day-night cycle of 16 hr light and 8 hr dark with lights off at 1030. Food and water were available at all times.

Apparatus.

Tests for copulatory behavior were conducted in the home cages of the males. Behavioral data were recorded on an Esterline-Angus Event Recorder.

Procedure.

To induce sexual receptivity, stimulus females were injected with 60 ug estradiol benzoate (EB) approximately 72 hr before testing and 600 ug progesterone approximately 6 hr before testing. Tests were begun with the introduction of the female into the male's home cage 4 hr after the lights went out. The room in which the tests were conducted was illuminated with a 25 watt red bulb.

Male copulatory behavior in P.m. bairdi is comprised of mounts (with thrusting), intromissions (with vaginal insertion), and ejaculations. The male is capable of achieving multiple ejaculations within a given time period. The temporal pattern of the behavior is such that each copulatory series is comprised of several intromissions and terminates with an ejaculation. Following ejaculation there is a period of sexual quiescence (post ejaculatory interval) before the next copulatory series is initiated. A mating test was terminated when one of the following criteria had been satisfied: (1) 30 min after the start of the test with no intromission; (2) no ejaculation within 20 min of the first intromission of a copulatory series; (3) no intromission within 15 min after completion of the first copulatory series; (4) completion of two copulatory series. Both before and after castration males were tested once a week. Following castration, if the males failed to exhibit any sexual response on three consecutive copulatory behavior tests they were

no longer tested and automatically scored as sexually unresponsive for the remainder of the experiment.

Measures.

During each behavioral test the following copulatory measures were recorded: mount latency (ML)- time in seconds from introduction of the female to the first mount or intromission, whichever came first; intromission latency (IL)- time in seconds from introduction of the female to the first intromission; ejaculation latency (EL)- time in seconds from first intromission of a copulatory series to an ejaculation; intromission frequency (IF)- number of intromissions in a copulatory series; mount frequency (MF)- number of mounts in a copulatory series; mean interintromission interval (MIII)- mean interval in seconds between intromissions in a copulatory series including the interval between the last intromission and ejaculation. For the intact males, intromissions were followed by a brief period of sexual inactivity (grooming, exploration, digging), whereas a mount was followed almost immediately by another mount attempt until an intromission was achieved. In contrast, there were many instances in castrated deermice in which a mount or cluster of mounts and intromissions was followed by a brief period of sexual inactivity not distinguishably different from that seen after intromissions in intact males. Sachs and Barfield (1970) employed the term "mount bouts" to identify a similar clustering of mounts and intromissions observed in rats. After castration we recorded mount bout frequency (MBF)- number of mount bouts in a copulatory series; and mean intermount bout interval (MIMBI)- mean interval in seconds between mount

bouts including the interval separating the last mount bout and ejaculation. The abbreviation for a measure followed by a hyphen signifies the copulatory series to which the measure refers (i.e. MF-2).

Data Analysis.

Comparisons of the percentage of males no longer exhibiting ejaculation, intromission or mounting behavior on each week following castration were made using a Chi-square test. In order to further analyze the behavioral data, each male for each of the copulatory measures was assigned a score equal to the mean of his precastration behavior tests in which ejaculation occurred and another score equal to the mean of his postcastration behavior tests in which ejaculation occurred. Within-subject comparisons of copulatory performance among ejaculating males before and after castration were conducted by using a matched-pairs T-test. Finally, data from castrated males were collected so that one set of data was composed of the males' first behavior test following castration in which ejaculation occurred, the second set of data was composed of the males' last behavior test following castration in which they ejaculated, and the final data set was composed of the males' first behavior test in which they failed to ejaculate, but in which intromissions were still being achieved. One-way analysis of variance was conducted on these sets of data. When the assumption of homogeneity of variance was violated log transformations were performed. Significant F ratios were followed by the Student-Newman-Keuls procedure (Winer, 1962).

RESULTS

The percentage of males maintaining ejaculation, intromission and mounting behavior in successive weeks following castration is illustrated in Figure 1. By the fourth week after gonadectomy 80% of the males failed to ejaculate. Further analysis revealed that the number of males that had lost the ejaculatory response by weeks 4 and 5 was significantly greater than the number in which intromission had disappeared (Week 4, $X^2(1)=4.20$, $p<.02$; Week 5, $X^2(1)=3.72$, $p<.05$). Also, the number of males who were no longer exhibiting intromission by weeks 3 and 5 was significantly greater than the number of males who were no longer exhibiting mounting behavior (Week 3, $X^2(1)=3.06$, $p<.05$; Week 5, $X^2(1)=3.06$, $p<.05$). It should be noted that failure to exhibit copulatory behavior one week did not necessarily mean that the male would fail to exhibit behavior in the following week.

In Table 2 the copulatory performance of males achieving ejaculation following castration is compared with their precastration performance. Time measures increased significantly following gonadectomy (ML, IL, EL, MIII, and MIMBI), as did MF. After castration IF-1 and IF-2 were significantly less than before castration, whereas MBF-1 and MBF-2 were no different from precastration levels.

In order to further assess the behavioral changes which occurred after castration, comparisons of copulatory performance were made between castrated males' first and last test with ejaculation and their

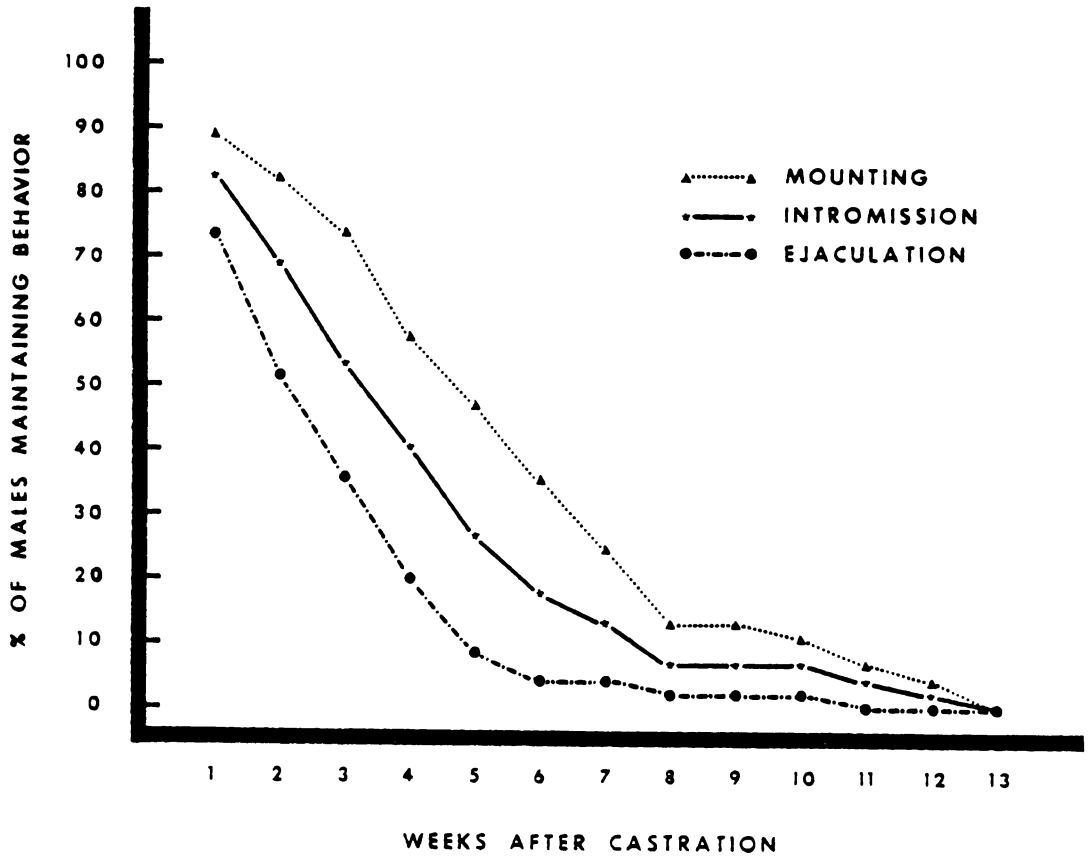

Figure 1. Percentage of male deermice maintaining mounting, intromission and ejaculatory responses on successive weeks following castration.

Table 2. Effects of Castration on Male Copulatory Performance[a]

Measure	Pre-Castration	Post-Castration	p[b]	N
ML (sec)	529 ± 39	747 ± 57	<0.001	33
IL (sec)	545 ± 41	789 ± 58	<0.001	33
MF-1	2.1 ± .5	9.3 ± 2.0	<0.001	33
IF-1	12.8 ± 1.0	9.6 ± .8	<0.05	33
MB-1	12.8 ± 1.0	11.9 ± .8	ns	33
EL-1 (sec)	354 ± 20	430 ± 29	<0.05	33
MIII-1 (sec)	31.3 ± 2.1	60.5 ± 8.9	<0.001	33
MIMBI-1 (sec)	30.0 ± 2.0	41.7 ± 4.3	<0.001	33
PEI (sec)	400 ± 17	419 ± 15	ns	25
MF-2	1.5 ± .4	4.2 ± 1.5	<0.05	20
IF-2	11.1 ± .7	8.8 ± 1.0	<0.05	20
MB-2	11.1 ± .7	9.8 ± 1.0	ns	20
EL (sec)	141 ± 9	182 ± 17	<0.05	20
MIII-2 (sec)	12.2 ± .8	22.1 ± 1.9	<0.001	20
MIMBI-2 (sec)	12.0 ± .9	18.1 ± 1.6	<0.001	20

Note. ML= Mount latency; IL= Intromission latency; MF= Mount frequency; IF= Intromission frequency; MB= Mount bout frequency; EL= Ejaculation latency; MIII= Mean interintromission interval; MIMBI= Mean intermount bout interval; PEI= Post ejaculatory interval

[a]Mean scores (±SEM) only for animals which ejaculated
[b]Two-tailed matched-pair T-test

first test following the loss of ejaculation in which intromissions occurred. Results are presented in Table 3. In castrated males' first test after losing ejaculation MIMBI was significantly longer than both the first and last test with ejaculation. Also, MIII of males who were no longer ejaculating was significantly longer than the castrated males' first test with ejaculation. However, MIII in the last test before the ejaculatory response disappeared did not differ from either of the other groups. In both the last test with ejaculation and the first test in which ejaculation did not occur MF was significantly increased over the first test with ejaculation. There were no differences between the groups in IF, MBF or IL. Also, there was no difference in EL between the two groups of ejaculating males.

Table 3. Comparison of Copulatory Performance Among Castrated Male Deermice Before and After the Disappearance of Ejaculation

Measure	EJACULATION PRESENT		EJACULATION ABSENT		
	First Test (1)	Last Test (2)	Intromissions Only (3)	F	Significant Individual Comparisons
IL	784 ± 75[a]	710 ± 90	962 ± 122	1.71	-----
MF	7.3 ± 2.4	13.6 ± 3.0	24.7 ± 6.5	5.68*	1 < 2,3
IF	11.3 ± 1.1	9.1 ± 1.4	7.9 ± 1.6	1.73	-----
MBF	12.6 ± 1.1	12.3 ± 1.4	12.1 ± 2.3	<1	-----
MIMBI (sec)	35.8 ± 3.6	45.4 ± 4.6	78.6 ± 12.8	10.1**	1,2 < 3
MIII (sec)	45.2 ± 6.7	71.6 ± 12.3	97.4 ± 12.0	7.1	1 < 3
EL (sec)	425 ± 38	473 ± 46	-----	<1	-----
N	22	22	15		

[a] mean scores (±SEM)

*P < .01

**P < .001

EXPERIMENT 2

The first experiment established that the expression of male copulatory behavior in male deermice depends upon the secretion of gonadal hormones. The purpose of Experiment 2 was to investigate the role of T and two of its major metabolites, E and DHT, in the mediation of male copulatory behavior in P.m. bairdi. Castrated males were treated with these hormones to determine whether sexual behavior could be reinstated.

METHOD

Subject Assignment and Hormone Treatment.

The Subjects were 32 P.m. bairdi from Experiment 1. Males were matched according to the number of postcastration tests required to reach the criterion of three successive weeks without exhibiting any sexual behavior and assigned to one of four hormone treatment groups. Beginning on the morning after their third unsuccessful mating test in Experiment 1, males received daily subcutaneous hormone injections for six weeks. The treatments used were: 200 ug testosterone propionate (TP); 200 ug 5α-dihydrotestosterone propionate (DHTP); 2 ug estradiol benzoate (EB); or sesame oil (OIL). Hormones were dissolved in .02 cc sesame oil. The 200 ug dosage of TP was selected on the basis of preliminary data which indicated that 100 ug TP was ineffective in

restoring sexual behavior, 200 ug TP was highly effective, and 400 ug TP increased mortality. In the course of the study one DHTP and one EB animal died.

Procedure.

The males were tested once a week for sexual behavior during hormone therapy. Testing procedures, behavioral measures recorded and preparation of stimulus females were the same as those employed in Experiment 1. The males were sacrificed and weighed after the sixth behavioral test. The seminal vesicles and ventral prostate gland were removed, cleaned of all adipose tissue and weighed on a Mettler balance to the the nearest mg.

Data Analysis.

All behavioral data and histological data were analyzed with Mann-Whitney U tests.

RESULTS

The percentage of males displaying mounts, intromissions and ejaculations for each of the six sexual behavior tests is illustrated in Figure 2. TP and DHTP were equally effective in restoring mounts, intromissions and ejaculations. The percentage of EB-treated males exhibiting mounting was intermediate between the androgen treatment groups and the OIL controls. In the EB group, animals displaying mounting on a given test did not necessarily continue to show mounting on subsequent tests. However, six out of seven EB-treated males displayed mounting on at least one test. EB was minimally effective in restoring intromission and totally ineffective in activating ejaculatory behavior.

Table 4 presents data from tests in which copulation occurred. TP-treated males took significantly longer to initiate copulation than DHTP males. On all other copulatory measures, the two groups did not differ. Whereas TP and EB males did not differ in ML or IL, males receiving EB exhibited significantly more mounts and fewer intromissions than TP males. EB males tended to cluster their mounts into mount bouts and a mean mount bout frequency of 9.4 was obtained.

There were no differences in body weight among the different treatment groups, with the mean body weight for TP, DHTP, EB and OIL males being 18.8, 19.2, 18.2 and 18.1 g respectively. TP and DHTP males did not differ in mean combined seminal vesicle-ventral prostate weight

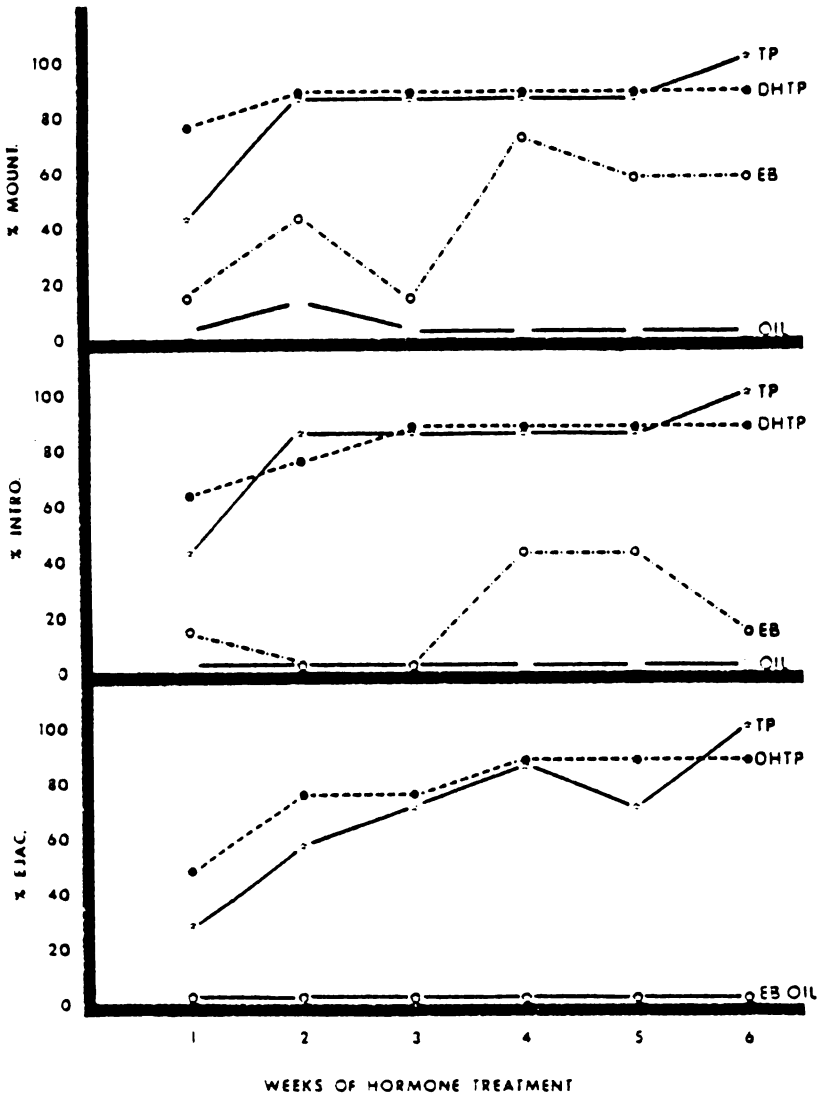

Figure 2. Percentage of castrated male deermice exhibiting mounting, intromission and ejaculation on successive weeks after onset of daily treatment with 200 ug TP, 200 ug DHTP, 2 ug EB or sesame OIL.

(237 and 274 mg respectively), but both were significantly heavier ($p < .0001$) than the EB and OIL males (20 and 24 mg respectively).

Table 4. Effects of Hormones on Mating Performance of Castrated Male Deermice

Measure	TP[a]	DHTP[a]	EB[b]
% Tests with M/I/E (%)[c]	81/81/69	83/81/75	43/19/0
ML (sec)	564 ± 115	301 ± 38*	751 ± 169
IL (sec)	576 ± 122	309 ± 39*	928 ± 215
MF-1	2.6 ± 1.1	3.6 ± 1.3	41.4 ± 8.6**
IF-1	19.0 ± 3.5	15.0 ± 2.5	3.5 ± 1.6**
EL-1	489 ± 54	378 ± 70	---
PEI (sec)	421 ± 23	440 ± 53	---
MF-2	1.2 ± .4	.6 ± .2	---
IF-2	12.9 ± 1.7	11.5 ± 1.5	---
EL-2	162 ± 16	152 ± 30	---

[a]Mean scores (±SEM) only for animals which ejaculated

[b]Mean scores (±SEM) only for positive responding animals

[c]Percentage of tests on which mounts, intromissions, or ejaculations occurred

*P<0.05 vs TP

**P<0.01 vs TP

DISCUSSION

The removal of gonadal hormones by castration resulted in a decline in male sexual behavior of P.m. bairdi with ejaculation disappearing first, then intromission, and, finally, mounting. The complete pattern of male sexual behavior (mounting, intromision, and ejaculation) was restored by the administration of either TP or its 5α-reduced metabolite, DHTP. In contrast, EB restored mounting behavior, but was only minimally effective in restoring intromission and did not induce any ejaculatory responses. TP and DHTP were both equally effective in restoring male copulatory behavior in castrated deermice. Both groups of males responded similarly on all measures of copulatory performance except for DHTP males having a shorter latency to initiate copulation than TP males.

The disappearance of ejaculation before intromission observed in deermice following castration has also been reported to occur in guinea pigs (Grunt and Young, 1953) and rhesus monkeys (Phoenix et al., 1973). In male rats some investigators have found that intromissions were maintained after ejaculatory responses had disappeared (Beach and Holtz-Tucker, 1949; Stone, 1939), although others have reported that ejaculations and intromissions disappeared simultaneously (Davidson, 1966; Larsson, 1966). In addition to deermice, mounting response have been reported to continue after intromissions have disappeared in rats

(Davidson, 1966), hamsters (Beach and Pauker, 1949), guinea pigs (Grunt and Young, 1953), rabbits (Stone, 1932), dogs (Beach, 1970; Hart, 1968), cats (Rosenblatt and Aronson, 1958) and rhesus monkeys (Phoenix et al., 1973).

The results of the hormone replacement study are similar to those reported for guinea pigs which also repond equally well to TP or DHTP treatment (Alsum and Goy, 1974). In all other species in which DHT(P) activated the complete male sex behavior pattern, it was not found to be as potent as T(P): hamsters (Whalen and DeBold, 1974); Swiss Webster mice (Luttge and Hall, 1973); rabbits (Agmo and Sodersten; 1975; Beyer and Rivaud, 1973); and rhesus monkeys (Phoenix, 1974). Moreover, the observation that DHTP was at least as potent as TP in stimulating seminal vesicles and ventral prostate gland agrees with studies on rats (Whalen and Luttge, 1971), two strains of mice (Luttge and Hall, 1973) and hamsters (Payne and Bennett, 1976).

In the present study EB stimulated a high frequency of mounting behavior in six out of seven animals. Higher doses of EB resulted in the animals becoming very lethargic (Pomerantz, unpublished observations); therefore, it would appear unlikely that intromission and ejaculation of castrated male deermice were not facilitated due to inadequate levels of E. Among other species in which DHT(P) promoted sexual behavior, EB failed to activate sexual behavior in guinea pigs (Alsum and Goy, 1974), rhesus monkeys (Phoenix, 1978) and rabbits (Beyer et al., 1975). However, hamsters (DeBold and Clemens, 1978; Noble and Alsum, 1975) and Swiss Webster mice (Edwards and Burge, 1971) responded to EB in a fashion similar to deermice (i.e. exhibiting a high

frequency of mounting and only rarely intromitting). The failure of EB to restore intromissions or ejaculation in these species may be related to the inability of EB to stimulate genital structures. However, this is in contrast to the activation of the complete copulatory pattern by EB in castrated rats (Sodersten, 1973) and deer (Fletcher, 1978). Additionally, EB-induced mounting behavior may depend on adrenal secretion. In castrated male rats being treated with EB, adrenalectomy prevented ejaculations; however, adrenalectomized males continued to mount (Gorzalka et al., 1975).

Species differences or similarities in the ability of T's metabolites, DHT and E, to induce male sexual behavior may reflect a varying degree of reliance on T metabolism by 5α-reduction and aromatization respectively. It is noteworthy that castrated males in two cricetid rodent species, deermice and hamsters, responded similarly to EB administration, exhibiting mounting and, infrequently, intromission. In both species DHT(P) administration stimulated the full copulatory pattern; however, DHTP was a more potent activator of male sexual behavior in deermice than in hamsters. It remains to be determined whether metabolism of T to DHT (5α-reduction) or to E (aromatization) is necessary for T activation of male copulator behavior.

Castration had a pronounced effect on the timing of male copulatory behavior in male deermice. This influence may have affected other components of copulatory performance. In comparison to precastration levels, castrated deermice exhibited a substantial increase in interintromission and intermount bout intervals, and a concomitant decrease in the number of intromissions preceeding ejaculation. This

rise in MIII and MIMBI observed in deermice following castration may be related to their ability to attain an ejaculation with fewer intromissions than were necessary for ejaculation before castration. Castrated rhesus monkeys also exhibited an increase in interintromission interval and a decrease in the number of intromissions preceeding ejaculation when compared to precastration levels (Michael and Wilson, 1974). After castration male rats achieved an ejaculation in fewer intromissions than before castration, but no increase in interintromission interval was observed (Davidson, 1966; Larsson, 1966). However, in intact male rats when the interintromission interval was lengthened beyond normal limits, males needed fewer intromissions to achieve ejaculation (Bermant, 1964; Hard and Larsson, 1970).

The interval separating intromissions and/or mount bouts also appeared to be a factor in the disappearance of the ejaculatory response among castrated male deermice who were still displaying intromissions. Their inability to achieve ejaculation could arise from their increase in interintromission and intermount bout intervals beyond a limit necessary to achieve an ejaculation. Although not directly analagous, in intact rats ejaculations were prevented by experimentally enforcing interintromission intervals of greater than 10 minutes (Larsson, 1960).

In summary, castration of male deermice resulted in a decline in male sexual behavior with ejaculation disappearing first, followed by intromission and, finally, mounting. Subsequent hormone replacement therapy with TP or its 5α-reduced metabolite, DHTP, reinstated all aspects of male sexual behavior. Treatment with the aromatized metabolite of TP, EB, was only effective in restoring mounting behavior. It

is suggested from these results that there is a greater likelihood that T may mediate male sexual behavior through 5α-reduction to DHT than through aromatization to E.

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