Models of Early Hormonal Effects on Intrasex Aggression in Mice

Frederick S. von Saal

INTRODUCTION

Aggression is a term that has been applied to many different types of behaviors, from hostile language and gestures to physical violence (Buss, 1961). Aggression, as used here, will refer to a category of behaviors associated with physical attack by one house mouse (male or female) on another mouse of the same sex. This type of aggression is therefore most appropriately referred to as "intrasex" aggression. But conspecific aggression in mammals is often referred to as "intermale" aggression, since fighting is generally considered to be a trait characteristic of males and uncharacteristic of females. An exception to this general statement has been the recognition that many, but not all, female mammals exhibit aggression during the postpartum period in defense of their young (Svare, 1981). It is important to recognize that other types of conspecific aggression (e.g., fear-induced aggression, sex-related aggression, infanticide) are commonly observed in many mammals. These other forms of conspecific aggression are influenced by variables different from those that influence either intermale or interfemale aggression (Moyer, 1974). For example, when a nonreceptive female mouse is placed into the home cage of a sexually experienced adult male, the male will attempt to mount the female and the mounting attempts will be rejected. As a result, the male often becomes highly aroused and attacks the female (von Saal & Bronson, 1978). Male mice normally do not attempt to mount females that are not in estrus, but a male that is isolated, except for occasional opportunities to mate with a receptive female, will become highly aroused if any female is placed in its cage. Aggression by a male toward a nonreceptive female may thus reflect the response of a highly aroused male to being frustrated in its attempts to mate. It is therefore necessary to specify the particular type of aggression one is referring to when discussing aggression in mammals.

Frederick S. von Saal • Division of Biological Sciences and Department of Psychology, University of Missouri, Columbia, Missouri 65211.
Scott and Fredericson (1951) have termed behaviors that occur when two animals come in conflict “agonistic behaviors.” The two most obvious agonistic behaviors are attack and escape. Under the appropriate conditions, aggression between mice can be very easily identified and quantified. Intrasex aggression in house mice, Mus musculus, can be divided into a number of distinct behaviors. When placed together, two male or two female mice will sniff and groom each other, with the grooming by one mouse often becoming more and more intense. At the same time, an increase in general arousal may occur, as evidenced by an increase in general activity. Tail rattling (vibrating of the tail) quite commonly precedes an attack, which is typically aimed at the flanks of the opponent.

MASCLINIZATION AND DEFEMINIZATION

Sexual differentiation commences in mammals during the early fetal period (Jost, 1972). If the gonads have differentiated into sexes as a result of the presence of a Y chromosome (Wachtel, 1977), androgens are secreted by the interstitial cells. Exposure of males to suprathreshold levels of androgens during the time that specific target tissues are differentiating profoundly influences the development of these tissues. It has now been demonstrated that within the preoptic area of the hypothalamus of rats, prenatal and neonatal androgen exposure alters both the timing and number of cell divisions in an area referred to as the “sexual dimorphic nucleus” (Gorski, Harlan, Jacobson, Shryne, & Souham, 1980; Jacobson & Gorski, 1980; Jacobson, Shryne, Shapiro, & Gorski, 1980). The pattern of synaptic connections within the preoptic area is also different in male and female rats as a result of perinatal androgen exposure (Raisman & Field, 1973). Thus, androgen exposure during the period of sexual differentiation influences brain morphology in rats. It seems reasonable to speculate that these morphological differences could lead to differences in brain function and thus in behavior.

Two extensively studied behaviors that are modulated by prenatal and neonatal androgen titer in mice are copulatory behavior and intermale aggression. Since androgens influence both brain development and differentiation of the external and internal reproductive organs, one problem that immediately became apparent to researchers was that of separating central from peripheral effects of androgen exposure during early life on adult sexual performance (Reich, 1945; Lutge, 1929). In contrast, intermale aggression provides a model behavior that is sexually dimorphic, is influenced by different variables in males and females, and is not dependent on specific anatomical structures, such as a penis or vagina, to be exhibited normally. Aggression therefore has been utilized as a model behavior to assess the role of androgens in the ontogeny of masculine behavior in species such as the house mouse in which adult males of most strains are found to be highly aggressive when placed together (Simon, 1979). While useful for studying the process of masculinization, the study of the ontogeny of intermale aggression cannot be utilized to assess the role of gonadal steroids in the defeminization process, that is, the loss of the potential to exhibit female
behaviors. Differentiation has been proposed to be an independent process that does not merely reflect the degree to which an animal is masculinized (Bench, 1975; Whalen, 1974).

The following section will briefly review experiments supporting some different models concerning the role of androgen exposure during early life on aggression between male mice. Research that I have conducted concerning the influence of intrauterine positioning of male and female fetuses on fetal hormone titers and adult behavior of both male and female mice will then be discussed in relation to models concerning the role of the early hormonal environment on both intermale and interfemale aggression.

THE ONTOGENY OF INTERMALE AGGRESSION IN MICE

Androgen secretion in male mouse fetuses has been reported to commence on about Day 13 of gestation (Block, Lew, & Klein, 1971; Rugh, 1968). Differentiation of the Wolffian ducts and external genitalia into the male pattern commences during prenatal life and continues into the early neonatal period. At birth, androgen levels in male mice are low and do not begin to increase again until approximately one month of age. At this time, plasma androgen levels begin increasing and in many strains reach maximal values between 60 and 70 days of age and then decline somewhat (McKinney & DeJardins, 1973; Selmanoff, Goldman, & Ginsburg, 1977; vom Saal & Bromson, 1980a). The testes, seminal vesicles, prostate, and preputial glands go through a period of development at puberty (the onset of the capacity to reproduce), which occurs between Days 40 and 50 after birth. It has been reported that the onset of intermale aggression in intact male mice is correlated with the increase in androgen output by the testes at puberty. The onset of intermale aggression has been reported to occur around Day 35 in intact male mice, somewhat before the successful insemination of females. However, the aggression exhibited by juvenile males is less intense (as measured by the latency to attack, number of attacks and duration of fighting) than that observed in older males (Barclay & Goldman, 1977a; Fredericson, 1950; McKinney & DeJardins, 1973; McKinney & Ingle, 1974).

The onset of aggressive behavior in male mice is correlated with an increase in the percentage of circulating androgen that is present as testosterone rather than a 5α-reduced androgen (e.g., dihydrotestosterone). By adulthood, testosterone accounts for about 75% of the androgens in the plasma (McKinney & DeJardins, 1973). One of the earliest studies relating testosterone levels to aggression was reported by Beeman (1947). She found that castrating male mice at ages ranging from 23 to 85 days resulted in a complete absence of fighting (as well as other behaviors associated with fighting, e.g., rough grooming and tail rattling) in male mice if a minimum of 25 days elapsed between castration and the onset of behavior testing against a male opponent. When implanted with pellets containing testosterone propionate (TP), a longer-acting synthetic androgen than testosterone, the previously nonaggressive castrated males ex-
habitated aggression after four days of exposure to TP. Removal of the TP implant resulted in the animals again exhibiting no aggression when tested four days following removal of the implant. Subsequent experiments have confirmed the importance of circulating androgen for the induction of aggression in male mice that have not had previous experience fighting. But it has also been found that after male mice have become dominant or subordinate, regardless of the presence or absence of testosterone, dominant males will continue to be aggressive and subordinate males will exhibit submissive behaviors (Maruniak, Desjardins, & Bronson, 1977; Scott & Fredericson, 1951; vom Saal, unpublished observation). Thus, circulating titers of testosterone do not correlate with aggressiveness in mice that have had previous fighting experience (see Leshner, 1975; for a model proposing such a correlation). Learning also plays a major role in determining aggressiveness and dominance status in rhesus monkeys (Joslyn, 1973; Royama, 1967; Trimble & Herbert, 1968). In addition, prior experience fighting (and thus dominance status) influences other androgen-dependent behaviors such as infanticide and urine-marking (Maruniak, Desjardins, & Bronson, 1977; vom Saal, in press d; vom Saal & Howard, 1982).

Circulating testosterone induces a male to exhibit specific behaviors in response to appropriate environmental cues. In adult male mice, the exhibition of aggression is thus also influenced by the physical environment (e.g., is it the animal's home territory? Barfield, Busch, & Walten, 1975; Charpenier, 1969), the social environment (e.g., isolation versus group housing; Valzelli, 1969), and the perception of pheromonal cues (Dixon & Mackintosh, 1975; Mugford & Nowell, 1970, 1971).

**THE ORGANIZATION/ACTIVATION MODEL OF INTERNAL AGGRESSION**

Numerous experiments have provided support for the concepts that exposure to androgen during the neonatal period is necessary to organize the neural substrate mediating aggression so that aggression can be elicited by appropriate environmental cues when the organism is activated by exposure to androgen again in adulthood. The organization/activation model proposes that the stimuli for aggression would be ineffective in eliciting aggressive behavior without both organization during the neonatal critical period of neural differentiation and adult activation of the previously organized neural substrate by androgen. According to this model, therefore, male- and female-typical behavior patterns are determined by the hormonal environment during development but are not exhibited until activated by the appropriate hormones later in life (cf. Beatty, 1979).

The organization/activation model was borrowed from developmental biology. Of particular importance was the finding of Pfeiffer (1956) that female rats exposed to androgen through transplanted testicular tissue during the neonatal period were acyclic (i.e., did not exhibit estrous cycles) in adulthood, since implanted ovaries did not show any evidence of corpora lutea formation indicative of ovulation. Similar results were obtained with male rats castrated in adulthood and then implanted with ovaries. Castration of a male rat at birth,
however, resulted in ovaries implanted in adulthood showing evidence of a cyclic appearance of follicles and corpora lutea indicative of the female pattern of cyclic gonadotropin release (cf. Harris, 1964; Harris & Jacobson, 1932). Exposure to androgen during a critical period shortly after birth thus results in the absence of normal estrous cycles in rats (Corleski, 1979) and mice (Barracho & Lemahieu, 1954). This phenomenon, referred to as the "androgen sterility syndrome," demonstrated that the course of development of both neural and peripheral target tissues was altered by androgen during critical (restricted) periods in early life.

Behavioral scientists were attracted by the possibility that androgen-mediated differentiation of neural tissues governing sexually dimorphic behaviors such as aggression might occur during critical periods in development similarly to the differentiation of neuroendocrine mechanisms and peripheral androgen-sensitive tissues (e.g., the genitalia and accessory sex organs, liver, kidneys, etc.; De Moor, Vermeulen, & Heyns, 1973). The organization/activation model was thus applied to the development of the neural substrates mediating sexually dimorphic behaviors. The application of this model to behavior was first proposed by Young, Goy, and Phoenix (1964), based on experiments designed to determine the effect of neonatal androgen exposure on adult sex behavior in rats. Harris (1964) also proposed that in rats, differentiation of the genitalia and accessory sex organs occurs as a result of exposure to androgen during the prenatal period, but that differentiation of the neural substrate mediating sex behavior occurs as a result of exposure to androgen during the neonatal period. This model was subsequently applied to the ontogeny of immature aggressive behavior in mice.

Numerous experiments were conducted, utilizing mice, that were reported to demonstrate that neonatal androgen exposure was a necessary prerequisite for aggressive behavior to be activated by adult exposure to testosterone. One problem with all these experiments that became apparent later on was that behavioral testing was not conducted for a sufficiently long period of time. The critical period for organizing the neural substrate mediating aggression into the "male" pattern was hypothesized to commence at birth and terminate sometime during the second or third week after birth. However, the brain was hypothesized to become progressively less sensitive to the organizing action of androgen subsequent to birth.

In the study on the influence of androgen exposure during the neonatal period on adult aggressiveness in mice, females injected with androgen after birth have been utilized as model organisms since the hormonal milieu during development rather than genotype is presumed to be the mediator of sex differences in behavior. Specifically, Edwards (1969) reported that, when the females were again exposed to increasing doses of TP in adulthood, fewer female mice injected with 500 μg TP on Day 20 after birth exhibited aggression than females injected with TP on the day of birth. Brunson and Desjardins (1970) found that, when injected with 200 μg TP in adulthood, fewer female mice injected with 100 μg TP for 24 days exhibited aggression (and that fighting animals exhibited fewer attacks) than females injected with the same
dose when they were younger than 12 days old. The important aspect of these
data is that 24-day-old females usually weigh around 13 grams, which means
that they would have been receiving over 5 mg of TP. This is a very large dose
for a mouse and was considered strong evidence that the brain was no longer
capable of being organized by Day 24 in mice. Also, female mice injected with
500 μg TP when 21 days old did not exhibit aggression (Levy, 1954), whereas
male mice injected with 500 μg TP when 18 days old were induced to exhibit
aggression (Levy & King, 1953). These data indicated that by Day 18, mice are
sufficiently mature to exhibit aggressive behavior if plasma testosterone titer
increase above normal levels for this age, and if they have previously been
exposed to androgen during early life.

Conversely, the issue of the effect of early androgen exposure on adult
aggressive behavior has been addressed by castrating males at different times in
life. As mentioned previously, for aggression to be exhibited between male mice
without previous fighting experience, androgen must be present in the circu-
lation during the time of behavior testing. Therefore, in studies involving ca-
stration of naive male mice, replacement of androgen in adulthood is necessary
to induce aggression. Edwards (1969) reported that, when administered increas-
ing doses of TP in adulthood, more male mice gonadectomized on Day 10 of
life exhibited aggression than males gonadectomized on the day of birth. Peters,
Bronson, and Whitsett (1972) castrated male mice on Day 0, 2, 6, 12, or 40 of
life and then administered all animals varying doses of TP in adulthood. A
greater percentage of animals from the groups castrated on Day 6 or later showed
evidence of wounding when grouped four per cage for 3 days than did the
animals castrated before Day 5 after birth. Observation of the animals for the
first two hours following grouping revealed a clear difference between the Day
2 and 4 castrates, which exhibited virtually no aggression, and the Day 6 castrates,
which did exhibit aggression.

The conclusion drawn from the above studies utilizing both male and female
mice was that organization of the neural tissue mediating aggression occurred
during the first 2 to 6 days following birth. During this period a marked decrease
in the capacity of the neural substrate to be organized into the male pattern
appeared to occur, with the termination of the critical period for organization
supposedly occurring sometime prior to Day 24 of life.

THE SENSITIVITY MODEL OF INTERMALE AGGRESSION

The validity of the hypothesis that androgen exposure during a critical
period in early life is a necessary prerequisite for aggressive behavior in mice
to be induced by testosterone in adulthood was challenged by Edwards (1970). He
reported that injections of 100 μg TP to female mice from Days 30 to 49
after birth resulted in more of the TP-treated females exhibiting aggression than
non-TP-treated females when all mice were exposed to increasing doses of TP
and tested for aggression at 95 days of age. This finding provided clear evidence
against the concept of androgen-induced neural organization during a critical
neonatal period being a necessary prerequisite for the induction of adult ag-
gressive behavior in response to testosterone. However, this finding did not rule out the possibility that neural organization at some prior period was a necessary prerequisite for activation of aggressive behavior later in life.

The results of a number of experiments have demonstrated that prior organization of the neural substrate mediating aggression in mice is not necessary for the activation of aggressive behavior by testosterone exposure in adulthood. For example, Svare, Davis, and Gandelmann (1974) reported that female mice exposed to 500 μg TP for the first time in adulthood would exhibit aggression against an intruder male if the exposure period to TP continued for a longer period of time than had previously been attempted. Brain and Evans (1975) reported similar findings utilizing silastic implants of testosterone. Vom Saal, Gandelmann, and Svare (1975) sought to determine whether exposing female mice to 500 μg TP for the first time in adulthood, until they exhibited aggression, would reduce the duration of TP treatment needed to reinstate aggression after a 60-day interval without exposure to TP. The results suggested that no organization or permanent change in the sensitivity of the neural substrate mediating aggression to testosterone had occurred during the first adult TP-exposure period, since no reduction in the duration of TP exposure required to reinstate aggressive behavior was observed. But in this experiment each animal was administered TP during the initial test phase only until it exhibited aggression, with the result that the sensitization period of TP treatment differed in length for each animal. In contrast, Barkley and Goldman (1975b) reported that following the induction of aggression in adult female mice (not previously androgenized) by implanting a capsule containing 10 mg of testosterone (a high dose), a capsule containing 0.5 mg testosterone was effective in maintaining aggression. Without prior exposure to the 10 mg capsule of testosterone, however, the 0.5 mg capsule was ineffective in inducing aggression in female mice. These data indicate that sensitization of the neural substrate mediating aggression to testosterone can occur in adult mice. It seems unlikely that the mouse brain suddenly loses the capacity to be sensitized by exposure to androgen around Day 60 after birth, as the results of vom Saal et al. (1976) suggested. Instead, the findings of Edwards (1970), Svare et al. (1974), and Barkley and Goldman (1977a) indicate that, with respect to the influence of androgen on internalex aggression in mice, there is no definite critical period during which sensitization of the brain by androgen can occur and after which it cannot occur. In addition, sensitization to androgen during early life is not a necessary prerequisite for female mice to be induced to exhibit internalex aggression when treated with androgen for the first time in adulthood.

The demonstration that organization of neural substrates prior to adulthood is not a necessary prerequisite to the induction of aggression toward a male or androgenized female opponent in female mice treated with TP for the first time in adulthood leads to the conclusion that the organization/activation model is not appropriate for describing the mechanism of action of androgen on the neural substrate mediating internalex aggression in mice. As an alternative, a model based on the concept of a continuous decrease in the sensitivity to androgen of specific neural areas from birth through adulthood seems more ap-
appropriate. According to this sensitivity model, exposure to androgen at any time in life results in an increase in the sensitivity of the neural substrate mediating aggression to subsequent exposure to androgen, with the sensitivity of the neural substrate to androgen being an inverse function of the time following birth that exposure to androgen first occurred. Without prior sensitization by exposure to androgen, the neural substrate is relatively insensitive to the aggression-inducing action of testosterone in adulthood, with the result that an extended period of exposure to a high dose of testosterone is required to induce aggression. This concept is not novel, since Beach (1945), writing with regard to sex behavior in rodents, had stated:

The sex hormones, in so far as they enter the behavioral picture, are best regarded not as stimuli or as organizing agents, but as chemical sensitizers which alter the stability of critical mechanisms within the neural nervous system. (p. 400)

The model based on diminishing sensitivity, as opposed to that based on the concept of a critical organizational period, led to the prediction that exposure to androgen during prenatal life, as well as during postnatal life, would alter the sensitivity of the neural substrate mediating aggression to androgen in adulthood. Since it had been reported that males castrated at birth do not exhibit aggression in response to androgen administration in adulthood (cf. Peters et al., 1972), it was assumed that prenatal exposure to androgen, which commences on Day 13 of gestation in male mice, was without effect on subsequent responsibility to androgen in adulthood. As described above, this conclusion was based on experiments which did not allow the animals to be exposed to androgen for a sufficient period of time prior to aggression testing. To test whether prenatal androgen exposure influenced adult aggression, 1.5 mg TP was injected daily into pregnant mice from Day 12 through Day 16 of pregnancy to masculinize the female fetuses and possibly supermasculinize the male fetuses. Other pregnant females were administered oil or remained undisturbed. All males and females from these litters were then gonadectomized at birth and in adulthood implanted with silastic capsules containing 5 mg testosterone and tested for aggression against an olfactory-bulbectomized male opponent. The duration of exposure to testosterone required to induce aggression against a male opponent was significantly longer in the females not exposed to TP prenatally than in males or the females that had been exposed to androgen during postnatal life and were thus more sensitive to androgen in adulthood. As part of this experiment, offspring of both sexes from TP-treated or untreated mothers were gonadectomized at birth and injected with 100 μg of TP on the next day. The TP injection on the day following birth had the effect of rendering all of these mice more sensitive to the aggression-inducing action of testosterone in adulthood than mice experiencing only prenatal androgen exposure. It appears, therefore, that while prenatal exposure to androgen can alter subsequent responsibility to androgen, the period during which the brain is most sensitive in this regard is around the time of birth (vom Saal, 1979).
PRENATAL ANDROGEN EXPOSURE: DIRECT (ORGANIZATIONAL) AND LATENT (SENSITIZING) EFFECTS ON BEHAVIOR

One aspect of the sensitivity model which may be incorrect is that exposure to gonadal steroids during early life in mice has only latent effects on behavior. It now appears that during prenatal life in mice, gonadal steroids have both direct (organizational) effects on behavior that are observed in the absence of gonadal secretions in adulthood and latent (sensitizing) effects on behavior that are apparent only after "activation" of the sensitized neural area by specific hormones during later life. In both dogs and monkeys, some sexually dimorphic behaviors have been found to be organized by androgen during prenatal life and not to require activation by androgen to be exhibited, while other behaviors are observed only after activation by androgen. For example, Beach (1975) has reported that in beagles, the leg-diff urination posture is organized into the male pattern by exposure to androgen during early life and does not require adult exposure to testosterone to be exhibited. Mounting, on the other hand, is exhibited only by beagles that have testes or are being treated with testosterone, and animals that have been sensitized by exposure to testosterone during early life are more likely to exhibit mounting than are animals not exposed to testosterone during early life. In infant rhesus monkeys, rough-and-tumble play, threat displays, and infantile sex behavior (rubbing and thrusting) are organized by androgen into the male pattern during prenatal life and do not require functional testes or treatment with testosterone to be exhibited by infant males. In contrast, in monkeys as well as dogs, rats, and mice, adult male copulatory behavior is influenced by both prenatal and adult androgen exposure, but activation by androgen is required for male sex behavior to be exhibited (Goy, 1988; Harlow, 1965). It has been proposed that in primates, androgen exposure during early life has both direct and latent effects, while in rodents, only latent, organizational effects are observed (Eaton, Goy, & Phoenix, 1973).

THE INTRAUTERINE POSITION PHENOMENON AND INTERMALE AGGRESSION

The positioning of fetuses during intrauterine development is an important source of variation in terms of the hormone titers that both male and female fetuses are exposed to in mice and rats and possibly in other polutous (multiple-birth) species. I have termed this the intrauterine-position phenomenon. To obtain animals from known intrauterine positions, female mice are time-mated, and their offspring are delivered by cesarean section and raised by foster-mothers (see vom Saal, 1981, for methods). The purpose of describing experiments in which both male and female mice from known intrauterine positions were compared for their behavior is that aggressiveness among males and among females has been found to be influenced by their prior intrauterine position. This phe-
vom Saal has thus proven to be a unique, naturally occurring experimental model system for examining the relationship between fetal hormone levels and adult behavior without the necessity of pharmacological intervention. In this regard, it is also important to remain aware that studies involving comparisons of animals from different intraterine positions are correlational and do not allow for firm cause-and-effect conclusions to be drawn.

On Day 17 of gestation, differentiation of the sex accessory ducts, external genitalia, and hypothalamus (Krogh, 1964) is occurring in fetal mice, and male mouse fetuses have three times as much circulating testosterone as do female fetuses at this time (vom Saal & Bronson, 1980a). In addition, on Day 17 of gestation, female mouse fetuses were found to have about 80% higher amniotic fluid levels of estradiol than male fetuses, and males located between two female fetuses (2M males) had about 50% higher amniotic fluid levels of estradiol than did males that developed between two male fetuses (2M males; vom Saal, Grant, McMullen, & Lauer, in press). 0M female fetuses also tended to have higher amniotic fluid levels of estradiol than 2M female fetuses (see Figure 1). Although the difference was not statistically significant (vom Saal & Bronson, 1980a), 0M and 2M male mouse fetuses did not differ significantly in their blood or amniotic fluid levels of testosterone, although 2M male fetuses did tend to have somewhat

![Diagram](https://example.com/diagram.png)

**Figure 1.** Schematic diagram of a mouse uterus showing the three potential intraterine positions that female fetuses can occupy relative to male fetuses: 2M Female, between 2 males; 1M Female, next to 1 male; OM Female, not seen at a glance. To determine the intraterine positioning of fetuses, mice are time-mated and the fetuses are delivered by cesarean section just before normal parturition. The young are then placed with foster mothers.
higher blood titers of testosterone than 0M male fetuses (vom Saal et al., in press). During the fetal period of sexual differen
tiation in humans, males also have significantly higher blood titers of testosterone than do females, and female fetuses have significantly higher blood titers of estradiol than do males (Belisle & Tulchinsky, 1980). Thus, the same pattern of sex differences in fetal steroid titers occurs in humans and mice.

The mechanism of transport of hormones between contiguous fetuses remains unknown. Based on behavioral data, Meisel and Ward (1981) concluded that in rats, steroids are transported between fetuses via the uterine blood vessels. Meisel and Ward claimed that blood flowed from the cervix toward the ovary in both the loop artery and the loop vein feeding each uterine horn (see Figure 1). This belief led to a comparison of animals that were labeled as upstream or downstream in this vascular scheme. Blood flow in the uterine arteries and veins in both the rat and the mouse is actually bidirectional (McLaren & Michie, 1966; vom Saal, unpublished observation). Meisel and Ward based their analysis system on a misinterpretation of an article (Del Campo & Gunther, 1972) that, in fact, did not address the issue of the direction of uterine blood flow as Meisel and Ward stated; their conclusion concerning the mechanism underlying the passage of hormones between fetuses is therefore invalid. It is considered likely that androgen and estrogen can diffuse across the amniotic and chorionic membranes surrounding each fetus. The amniotic fluid circulates through the gut during fetal life, and amniotic fluid titers of estradiol and testosterone are thought to be in equilibrium with the titers of these steroids in the fetal blood stream (Belisle & Tulchinsky, 1980). An important related observation is that during the last four to five days of gestation, mouse fetuses are tightly packed in each uterine horn, thus providing a large area of contact between the chorionic membranes of contiguous fetuses. In cattle, freemartin (sterile offspring) are found when male and female fetuses develop together in utero, a phenomenon thought to be due to vascular anastomoses between contiguous fetuses. Vascular anastomoses between contiguous fetuses have not been found in mice, however (Mar

The results of comparisons of males from different intrauterine positions suggest that exposure to different titers of estradiol results in variation in num-
merous characteristics relating to reproduction. In many experiments, only 0M and 2M males have been compared, since 1M males have always been found to be intermediate between 0M and 2M males in phenotype. In a comparison of their sexual performance, gonadally intact (i.e., not treated with hormones) 0M male mice exhibited significantly more mounts and intromissions than 2M males when placed for 30 minutes with a sexually receptive female. In rats, 0M males were also more sexually active than 2M males: 0M males exhibited more ejaculations to satiety (30 minutes without a mount) than did 2M males. There thus appears to be a decrement in sexual performance in 2M males relative to 0M males in both rats and mice (vom Saal et al., in press).

Of primary relevance to the current topic is the finding that intrauterine position influences different types of aggression in adult male mice, namely
intermale aggression and aggression toward infants (infanticide). Internmale aggression was examined in 0M and 2M male mice that had been castrated within one hour of cesarean delivery. The purpose of castrating the males at birth was (1) to eliminate any potential postnatal differences between 0M and 2M males in the titers of gonadal hormones to which they would have been exposed and (2) to compare 0M and 2M males for their aggressiveness while being treated with a known quantity of testosterone administered via silastic capsules. These 0M and 2M males were implanted with a silastic capsule containing 5 mg testosterone and were tested every other day for 10 minutes for aggressiveness (biting and chasing) toward a 1M male opponent that had been rendered anosmic via olfactory bulbectomy. The 2M males required a significantly shorter period of exposure to testosterone to exhibit aggression than did the 0M males. In addition, when autopsied after 35 days of exposure to testosterone, the 2M males had larger seminal vesicles than the 0M males (Vom Saal et al., in press). These findings indicate that adult 2M males are more sensitive than 0M males to the activational effects of testosterone in both the testicular substrate mediating intermale aggression and in the seminal vesicles.

The duration of exposure to testosterone required to induce aggression provides an index of aggressiveness in mice. Thus, 2M male mice appear to be more aggressive toward other males that do 0M male mice. But a correlate of an increased tendency to be aggressive in 2M males appears to be a decrease in sexual performance relative to 0M males. Taken together, these findings suggest that among male mice, the males that are the most aggressive toward other males should have the lowest sexual performance.

Another form of aggression, attack directed toward an infant by an adult (infanticide), has also been found to be influenced by intrauterine position in male mice. An adult mouse usually only attacks another adult of the same sex. In contrast, male CP-1 mice in my colony that do commit infanticide are equally likely to commit infanticide when placed with either newborn male or newborn female mice (Vom Saal & Howard, 1982). Gonadally intact 0M, 1M, and 2M male mice were compared for their behavior toward two newborn mice that were placed into each male's home cage for 30 minutes. The proportion of 0M, 1M, and 2M males that committed infanticide (killed the young) behaved parentally (retrieved the young to a nest and hovers over them), or ignored the young differed significantly: most 0M males committed infanticide, most 2M males behaved parentally, and 1M males were equally likely to behave parentally or commit infanticide (Vom Saal, in press a).

Infanticide is similar to intermale aggression in that unless the tests are present or testosterone is administered following gonadectomy, naive male mice do not commit infanticide, regardless of preconceptional position. When 0M and 2M male mice were castrated at cesarean delivery and treated with testosterone via silastic capsules in adulthood as described above, more 0M than 2M males began committing infanticide, while more 2M than 0M males behaved parentally toward newborn mice (Vom Saal, in press a). Thus, to observe differences between 0M and 2M male mice in behaviors that could influence reproductive fitness (infanticide, intermale aggression, and sexual performance),
either the testes have to be present or exogenously administered testosterone has to be present in the circulation. All of these findings are thus consistent with the sensitivity model described previously in that differences in behavior among adult males due to prior intrauterine position appear to reflect a latent difference in sensitivity to testosterone.

The finding that 0M males are the most likely to commit infanticide yet the least aggressive toward other adult males might at first seem surprising. But previous experiments have revealed that hormonal manipulations at the time of birth that lead to an increase in intermale aggressiveness lead to a decrease in infanticide; elevating testosterone levels at birth enhances intermale aggressiveness and decreases infanticide in mice (Gandelman & von Saal, 1977; Samuel, Jason, Mann, & Savare, 1981; von Saal, 1979). It is thus not surprising to find that there is a negative correlation in male mice between the tendency to be aggressive toward other adult males and the tendency to commit infanticide, although the adaptive significance of such a relationship is not readily apparent.

THE AROMATIZATION HYPOTHESIS

Estradiol Facilitates the Ontogeny of Male Sexual Behavior

The aromatization hypothesis refers to the proposition that testosterone serves as a prohormone that is converted (aromatized) to estradiol within target cells which contain aromatase enzymes. The estradiol that is produced by intracellular aromatization of testosterone is thought to interact with cytoplasmic estrogen receptors and then somehow to be translated into the nucleus where organizational or sensitizing effects of the hormone–receptor complex are exerted on the cell. The presumption has been that testosterone is required as a prohormone due to the fact that circulating estrogens are bound and thus inactivated by blood-binding proteins. Alpha-fetoprotein (AFP) is a protein that has been found in the blood of fetal and neonatal mice and rats, and AFP does bind estradiol with high capacity (MacClusky & Nafolun, 1981; McEwen, 1980).

Because of the hypothesis that circulating estrogens were inhibited from entering cells as a result of being bound by plasma proteins, circulating estrogens were not thought to influence the course of sexual differentiation in any mammal. Thus, while it has been known for some time that there are sex differences in estradiol tiers in human fetuses (Reyes, Boroditsky, Winter, & Faiman, 1974), this difference has not previously been thought to influence sexual differentiation in humans. One problem with ignoring the finding that there are sex differences in circulating estrogens during fetal life in humans in that with the exception of rodents, plasma proteins that bind estrogens have not been identified in other mammalian species (MacClusky & Nafolun, 1981). Also, AFP has actually been found inside brain cells in rats (Bembo & Williams, 1978; McEwen, Pippinger, Chapal, Gerlach, & Wallach, 1975), raising the possibility that even in rats and mice, AFP that is bound to estrogens may actually be actively transported into brain cells (perhaps by endocytotic mechanisms into specific neural
areas). I have proposed, therefore, that sex differences in fetal estradiol tiers (female fetuses have higher tiers than males) interact with sex differences in gonadal secretions of androgens (male fetuses have higher tiers than females) in regulating sexual differentiation. In addition, variation in phenotype among male and among female mice due to intrauterine position may be due to differences in both testosterone and estradiol tiers (vom Saal, in press c). Thus, the intrauterine position phenomenon is proposed to be mediated by both estrogens and androgens, rather than just androgens as previously believed (vom Saal & Bronson, 1980a).

Considerable research has been conducted to test the aromatization hypothesis. The effects of estrogen agonists and antagonists as well as inhibitors of aromatase enzyme activity (which block the conversion of testosterone to estradiol) have been examined. The dependent measure in virtually all of these experiments has been some aspect of sexual behavior: the rate or frequency of mounting, intromitting, or ejaculating or the capacity to exhibit proceptive or receptive behaviors typical of female rodents in estrus. The evidence is convincing that testosterone acts on the neural substrate mediating male sexual behaviors after conversion to estrogen within brain cells (MacCluny & Napolitano, 1981). For example, Sodersten (1979) has reported that exposure to estradiol during perinatal life appears to be necessary for the normal development of ejaculatory behavior in male rats. Thus, the findings that 0M male fetuses have higher tiers of estradiol than 2M male fetuses and that adult 0M male rats exhibit more ejaculations to satiety than 2M males are consistent with the hypothesis that exposure during early life to elevated tiers of estradiol enhances the development of male sexual behavior. Presumably, more estradiol passes from the circulation into brain cells in 0M male fetuses than in 2M male fetuses, thus increasing the intracellular pool of estradiol in 0M males. While 0M and 2M male fetuses do not differ significantly in their blood testosterone tiers, 0M males thus appear as if they had been exposed to high tiers of androgens relative to 2M males during fetal life, at least in terms of adult sexual behavior.

Estradiol Inhibits the Ontogeny of Intermale Aggression

Adult 2M male mice were more sensitive to testosterone in terms of the induction of intermale aggression and seminal vesicle growth, a finding that suggests that 2M males were exposed to higher tiers of testosterone than were 0M males during fetal life (exactly the opposite of the previous statement concerning sexual behavior). Since 0M and 2M male mice do not differ in their blood or amniotic fluid tiers of testosterone, but 0M males have elevated amniotic fluid tiers of estradiol, I have proposed that exposure to elevated concentrations of estradiol interferes with the effects of testosterone in both the neural tissues mediating intermale aggression and in the seminal vesicles during fetal life in males (vom Saal, in press c). Thus, 0M males have high tiers of estradiol relative to 2M males, and 0M males appear as if they had been exposed to an antiandrogen during fetal life. For example, administration of antiandrogens such as
cyproterone acetate during fetal life reduces aggressiveness in adult male mice (von Saal, 1976).

The above hypothesis might appear to be totally at odds with current ideas concerning the masculinizing effects of estrogens during early life (i.e., the aromatization hypothesis), but this is not in fact the case. As mentioned above, virtually all previous research concerning the effects of estrogens on sexual differentiation has involved examining sexual behavior rather than aggression. In the studies which have reported that an injection of estradiol benzoate into neonatal mice had the same effect on adult aggressiveness as testosterone (a finding that, if valid, would provide support for the hypothesis that testosterone is aromatized to estradiol in the neural areas mediating intermale aggression), very high doses of estradiol benzoate have been utilized. For example, Edwards and Herndon (1970) reported that an injection of 50 μg estradiol benzoate into newborn mice enhanced sensitivity to the aggression-inducing action of testosterone in adulthood. They concluded that during early life in mice, estradiol acted to organize the neural substrate mediating aggression, thus extending the aromatization hypothesis to include the ontogeny of aggressive behavior as well as sexual behavior. The conclusion drawn by Edwards and Herndon (1970) is obviously exactly opposite to what I have just proposed to be the effect of exposure to elevated tiers of estrogens during early life on intermale aggression in male mice. However, sexual behavior can be induced in an adult, 25-gram female mouse with an injection of 5 μg estradiol benzoate (a 0.2 mg/Kg dose). A newborn mouse weighs 1.5 grams, thus making a 50 μg injection equal to a dose of 33.3 mg/Kg (more than 150 times the dose required to activate sexual behavior in adult mice). Exposing animals at any time in life to massive doses of a steroid may produce effects that do not reflect the actual physiological role of the steroid. This is particularly true during perinatal life, since mice are thought to pass through a period of heightened sensitivity to the permanent effects of steroids on behavior around the time of birth (von Saal, 1979). Conclusions drawn from studies in which massive doses of a steroid are utilized are thus highly suspect, and it is possible that had doses of estradiol benzoate within a physiological range been utilized by Edwards and Herndon (1970), exactly the opposite results might have been obtained.

MODEL TESTING AND EXPERIMENTER BIAS

The bias inherent in model-testing often leads researchers to overlook or reject information that is not consistent with the current models. Such has been the case with the study of aggression in mice. Models concerning the hormonal control of aggression have strongly influenced both the types of questions that have been asked and the paradigms of the experiments designed to test empirically the validity of the models being tested. For example, it was hypothesized that male mice castrated at birth and female mice not treated with TP at birth would not be aggressive. Without this expectation, these animals might have
been tested for a longer period of time, and the hypothesis would have been rejected (cf. Edwards, 1969). There is little doubt that any observation involves some subjective component, and the experimenter bias that is inherent in observational research can be markedly influenced by current social theories. There is an interesting parallel, for instance, between male and female sex roles during the 1950s and early 1960s and the concept inherent in the organization/activation model that without the presence of estrous or vaginal secretions, females would be passive. Harlow, John, Senko, and Dopp (1956) exemplified this view in their description of the receptive posture assumed by female monkeys as indicating that the female role is one of a passive sexual partner submitting to the more dominant, active, sex-initiating male. The receptive posture in monkeys and many other primates is, at least superficially, similar to the posture assumed by a subordinate animal that is threatened by a more dominant animal. However, the behavior is also observed to be displayed as a means of recalling an infant that has strayed too far, by dominant males as a reassuring posture, and by animals that are soliciting grooming. Other views on this subject were expressed, of course. Inherent in Beach's (1945) argument—that a model based on sensitization rather than organization of neural areas during early life was appropriate for describing hormonal effects on behavior development—was the notion that there existed in adult males and females considerable plasticity in sex-related behaviors. Birch and Clark (1946) also argued that the belief that females were passive, based on the impression of an observer that the receptive posture resembled the submissive posture, was a blatant "projection of the Victorian idea of human sexuality into the realm of biological theory" (p. 330). They observed, for instance, that when a sexually experienced female chimpanzee presented to an inexperienced male and the male failed to mount her immediately, he was viciously attacked. It hardly seems reasonable to consider the receptive posture (which in this case is called soliciting behavior) as indicating passivity in light of this observation.

There is now little argument that females play an active, initiating role in copulation in many mammals that have been studied (Beach, 1976). It has also been proposed that in rodents, females may play an important role in the regulation of population size (vom Saal, 1981). The current view among psychologists and biologists is that in many species females play an important role in initiating copulation, as well as the learned recognition by population biologists that in many species females as well as males influence social structure and population dynamics, may thus actually be a reflection of, rather than the driving force behind, the changing attitude toward the role of women in Western societies over the last 10 to 15 years. In particular, the view of women as passive, submitting sex partners has changed radically.

With this thought in mind, a repeated observation led me to question both the notion that intact female mice are not aggressive and the relevance of the sensitivity model in aggression between female mice. I had observed that when adult female Rockland-Swiss or CF-1 albino mice were grouped together for the first time, at least one of the females would invariably attack and/or mount the other females. Initially, I was surprised by the consistency with which aggression
was observed between adult female mice after group-housing, as well as by the intensity of the aggression observed. Typically, it is stated that lactating female rodents are not aggressive (Scott & Fredericson, 1951). A survey of the literature revealed anecdotal reports that female mice had been observed fighting. But, because of the general belief that female mice were nonaggressive, these observations were usually discounted (cf. Anderson & Hill, 1965; vom Saal, in press b; White, Mayo, & Edwards, 1969). In some studies involving reproduction of mice in seminatural environments, females have been observed exhibiting aggression and taking part in territorial defense (Ladicky, 1976; Lloyd & Christian, 1999; Bolster & Petras, 1967). In general, though, male-male aggressive interactions have continued to be the focus in studies utilizing rodents.

THE INTRAUTERINE POSITION PHENOMENON
AND INTERFEMALE AGGRESSION

I hypothesized that the female mice that were exhibiting aggression toward other females might have been rendered aggressive due to exposure to elevated concentrations of testosterone during early life. This hypothesis was prompted by the report of Clements (1974) that female rats that developed in same between male fetuses had significantly longer anogenital spaces at birth than did female rats that did not develop contiguous to a male. In both rats and mice, anogenital distance at birth provides a sensitive bioassay for prenatal exposure to androgen, and the length of the space in males is almost twice that of females. In mice, anogenital distance of females at birth was also found to increase as a function of the number of male fetuses contiguous to a female during prenatal life. Females located between two male fetuses (2M females) showed greater distances than females located next to one male fetus (1M females), which in turn showed greater distances than females not located next to a male fetus (0M females; see Figure 1; vom Saal, 1976; vom Saal & Bronson, 1978). Subsequently, it was verified that 2M female fetuses have significantly higher titers of testosterone in both their amniotic fluid and blood than do 0M females during prenatal but not postnatal life (vom Saal & Bronson, 1980a).

The hypothesis based on the sensitivity model that adult 2M females should be more sensitive to testosterone as a result of exposure to elevated levels of testosterone during prenatal life was examined by Clements, Gadue, and Coniglio (1978). They found that 2M female rats exhibited higher mean frequencies than did 0M females when injected daily with 250 μg TP and tested with sexually receptive females at weekly intervals. This finding provided support for the sensitivity model described above, but the experiment was based on the assumption that adult females would have to be administered exogenous testosterone to activate androgen-sensitive neural areas and to observe the otherwise latent differences between 0M and 2M females. On the other hand, the observation that some intact female mice were highly aggressive while others appeared to be nonaggressive raised the intriguing possibility that prior intrauterine position, and thus differential exposure to testosterone (and estrogen) during pre-
natal life, might influence the tendency to exhibit interfemale aggression in mice. To answer this question, adult, intact OM and 2M female mice were matched for age and weight and housed in a cage divided into two living areas by a wooden partition. When both females were in diestrus, the partition was raised and the females were observed for 30 minutes. Of 28 pairs of females, biting attacks were observed in 14 pairs, and in 12 of these pairs the 2M female exhibited the attacks and established clear dominance over the OM female. In 6 more pairs, tail rattling, chasing, and rough (aggressive) grooming were observed, and in 5 of these pairs the 2M female exhibited these behaviors. Thus, in 17/20 pairs (85%) to which some aspect of aggression was observed, the 2M female exhibited aggression toward the OM female (Figure 2).

The intensity of aggression observed in intact female mice varies as a function of the estrous cycle. Hyde and Sawyer (1977) reported observing the highest levels of aggression (which, unfortunately, was not clearly defined) between females that were in proestrus and metestrus, which correlates with the time of the cycle during which progesterone levels are highest (Michael, 1976), suggesting a possible causal relationship. But OM and 2M females were compared for aggression when in early diestrus—that is, when both estrogen and progesterone levels are lowest. Although as yet untested, it is proposed that the difference in aggressiveness of OM and 2M females does not reflect a differential sensitivity to the activation effects of gonadal and/or adrenal steroids.

Lactating OM and 2M female mice were also compared for the tendency to attack an ovarietomized female intruder into their home territory on Day 7 following delivery of a litter. The intensity of the aggression exhibited toward

**Figure 2.** Comparison of aggressiveness in OM and 2M female mice. Postpartum aggression—the mean duration of time (± SEM) that 14 OM and 15 2M females that did not spend baring and chasing an intruder female during a 10-minute period when tested on postpartum Day 7 while nursing their young. Interfemale aggression—the percent of OM and 2M females that attacked and established dominance when OM and 2M females were paired for 30 minutes while in diestrus (based on 10 pairs in which aggressive behaviors were observed). Androgen-induced aggression—the cumulative percent of OM and 2M females that exhibited biting and chasing during 28 days of exposure to 5 mg testosterone contained in a silastic capsule. OM and 2M females were tested for 10 minutes every other day with a male intruder (15 2M and 9 OM; vom Saal, 1976b), or at weekly intervals with a sexually receptive female intruder (25 females per group; vom Saal & Bronson, 1978b). Different groups of OM and 2M females were used in these experiments.
a female intruder by the 2M females was significantly greater than that exhibited by the 0M females (Figure 2). Thus, both nonlactating and lactating 2M female mice are highly aggressive toward other females, while 0M females appear non-aggressive (vom Saal & Bronson, 1978).

Another interesting finding was obtained with 0M and 2M female mice were ovariectomized and implanted with silastic capsules containing testosterone. In this study, the 0M and 2M females were paired once per week for four weeks with a sexually receptive female in an attempt to replicate, in mice, the finding of Clemens et al. (1978) in rats. The proportion of 0M and 2M females that mounted was not significantly different, although somewhat more 2M females (91%) mounted after 28 days of testosterone exposure than did 0M females (84%; p = 0.08). But significantly more of the 2M females (74%) than the 0M females (44%) exhibited biting attacks toward the sexually receptive female (vom Saal & Bronson, 1978). In a previous experiment, ovariectomized 2M female mice had been found to require a shorter period of testosterone exposure to exhibit aggression toward a bulbectomized male than did 0M females (vom Saal, 1976). When compared in terms of the percentage of 0M and 2M females that exhibited aggression after 28 days of testosterone treatment when paired with either a sexually receptive female (vom Saal & Bronson, 1978) or a bulbectomized male (vom Saal, 1976), the data from these two studies are surprisingly similar (Figure 2). Since intact male mice do not usually exhibit aggression toward sexually receptive females, these findings raise questions concerning the validity of experiments that have utilized female mice as model animals for the study of hormonal influences on intermale aggression. It is possible that the stimuli that elicit aggression in intact male mice are different than the stimuli that elicit aggression in intact or testosterone-treated female mice. Bartles and Goldman (1978) also found that more adult female mice that were injected with TP or that received testosterone through silastic implants exhibited aggression toward a female opponent than did similarly treated males.

When viewed in isolation, all of the data from comparisons of the aggressiveness of 0M and 2M females suggest a fundamental biasing (organization) of the potential to exhibit aggression toward other females as a result of exposure to high concentrations of testosterone during prenatal life. For example, it appears that postpartum aggression in mice may be induced by direct neural stimulation, as a result of suckling by young, and that ovarian and pituitary hormones do not induce postpartum aggressiveness (Swartz, 1981). Thus, differences in the intensity of postpartum aggression based on prenatal intrauterine position cannot be viewed within the sensitivity model in which differences in adult behavior are presumed to reflect differences in sensitivity to the activation of hormones on the neural substrate mediating aggression. Instead of invoking the concept of differential sensitivity to hormones to account for differences in aggressiveness between 0M and 2M females, a more parsimonious approach is to propose that while the characteristics of the aggression exhibited by a female toward another female may vary depending on the physiological state of the attacking female, elevated levels of androgen during prenatal life exert organizational effects on specific neural areas, so that adult 2M females are more
aggressive than 0M females whenever the situation is such that aggression is observed. Intermale aggression, on the other hand, involves exposure to androgen during early life modulating the sensitivity of the neural substrate mediating aggression to the aggression-inducing effects of androgen in adulthood. Again, no such simple explanation can account for all of the results of comparisons of 0M and 2M female mice presented in Figure 2. Finally, it seems incorrect to view the action of testosterone as exerting a masculinizing effect on a 2M female's brain during prenatal life, since aggression toward females is not a typical masculine characteristic. Prenatal exposure to testosterone does not behaviorally masculinize 2M females. The 2M females are more aggressive than the 0M females, but unless they are lactating or are treated with exogenous testosterone in adulthood, this aggressiveness is directed only at other females and not at males (von Saal & Bronson, 1978). Findings based on comparisons of 0M and 2M females therefore appear most relevant to the study of the ontogeny of variability in “normal” female characteristics rather than as a model system for studying the process of masculinization.

It is interesting to speculate about the implications of the intrauterine position phenomenon to the reproductive ecology of mice. The findings from laboratory experiments conducted with 0M and 2M female mice have led to the prediction that the female mice that are dispersed from high-density populations in the wild are most likely 0M females. Since the great majority of dispersing animals are presumed to die (Lööcker, 1975), being highly aggressive should confer a substantial reproductive advantage of 2M females at high population densities (von Saal, 1981). A critical related finding is that the aggressive 2M females and nonaggressive 0M females do not differ in their basic capacity to produce and raise healthy young (von Saal & Bronson, 1978). But 0M and 2M females do differ in the timing of puberty (von Saal & Bronson, 1978), the length of estrous cycles during adolescence and in adulthood (von Saal & Bronson, 1980b; von Saal, Pryor, & Bronson, 1981), the age at which they cease producing live offspring (von Saal, Moyer, & Rines, 1982), their attractiveness to and their capacity to sexually arouse males (von Saal & Bronson, 1978), and their rates of urine-marking behavior. Urine marking serves to delineate territorial boundaries in mice (Harrington, 1976) and is correlated with dominance status (Martinjak et al., 1977), and 2M female mice mark a novel environment at significantly higher rates than do 0M females (von Saal & Bronson, 1978). Thus, 2M females appear to be more aggressive and possibly also more territorial than 0M females. While only 0M and 2M female mice have been compared in most studies, in all experiments in which 1M females have also been examined, 1M females have been intermediate in their characteristics—agenital distance at birth, the timing of puberty, and aggressiveness when treated with testosterone—between 0M and 2M females (von Saal, 1976, unpublished observations). Intrauterine position thus influences the morphology, physiology, and behavior of female mice. Since positioning of fetuses by sex in a uterine horn is a random process (von Saal, 1981), differences in aggressiveness due to intrauterine position cannot be related to differences in genotype. In contrast, individual differences in aggressiveness and sexual performance have been pro-
posed to be due to differences in genotype rather than differences in fetal hormone titers (cf. Chitty, 1967; Krebs, 1978). When taken together with the observation of Lloyd and Christian (1969) that only a few aggressive, dominant females in high-density populations of mice successfully produced surviving offspring (the subordinate females either failed to mate, failed to reach term if inseminated, or were unable to protect their young if they did carry the litter to term), my findings suggest that at high population density, the females that would be most likely to establish and defend a nest area and reproduce successfully would be the 2M females.

CONCLUSION

Based on the assumption that male mice are aggressive while female mice are passive, most researchers examining the effects of hormone exposure during early life on adult aggressiveness have focused on intermale aggression. It was assumed that male mice castrated at birth and female mice not treated with TP at birth would not be aggressive. This led numerous experiments to be conducted with too short a period of testosterone treatment and aggression testing. These experiments thus provided support for the organization/activation model of intermale aggression in mice. Subsequent experiments utilizing longer periods of treatment with testosterone have revealed that prior organization of the neural substrate mediating intermale aggression is not a necessary prerequisite for adult mice to be induced to exhibit intermale aggression when treated with testosterone. But exposure to testosterone during early life renders a mouse more sensitive to the aggression-inducing action of testosterone in adulthood, with the period of development during which testosterone has the greatest sensitizing effect being around the time of death. These findings provide support for a sensitivity model of intermale aggression—that is, exposure to androgen during early life exerts a latent (sensitizing) effect on the neural substrate mediating intermale aggression. Testosterone must be present in the circulation to induce (activate) a mouse to respond to the presence of a male opponent by exhibiting aggression.

The intraterine position phenomenon—the capacity of females to have their development modified by exposure to steroids secreted by contiguous fetuses—has proven to be a valuable model system for examining the relationship between endogenous differences in gonadal steroid concentrations during fetal development and behavior during later life. Relevant to the belief that females are generally nonaggressive is the finding that female mice that develop in utero between two male fetuses have elevated blood titers of testosterone during prenatal life and are highly aggressive toward other females but not males in adulthood. These females appear to have been organized into an aggressive phenotype by exposure to elevated titers of testosterone during prenatal life, but they cannot be considered to have been masculinized, at least in terms of aggressiveness. Male mice attack other males but not females, while the prenatally androgenized female mice are more aggressive only toward other females, not
males it is hypothesized that during early life in mice, androgens exert latent (sensitizing) effects on intermale aggression and direct (organizational) effects on interfemale aggression. Thus, intermale and interfemale aggression are un- 
der different hormonal and stimulus control in mice.

REFERENCES


Beach, F. A. (1978). Sexual orientation behavior in the male rat. Effects of castration and hormone admini- 


Berkovitz, E. (1969). A unitary fluid hormone. In N. Tschirschinsky & K. Brain (Eds.), Neural- 

Berman, E., & Williams, T. (1968). Evidence for intercellular localization of alpha-dopa- 

stration on the social dominance status of the female mouse strain. Psychoneuroendocrinology, 1968, 1, 300-331.


Brooke, E. J., & Berkovitz, E. (1969). Aggression and androgen administration in adult aggressive in- 


EARLY EFFECTS ON INTRASEX AGGRESSION


Simon, N. G. The genetics of maternal aggressive behavior in mice: Recent research and alternative strategies. Prenatal and Postnatal Development, 1979, 3, 97-108. (a)


vom Saal, F. S. Prenatal exposure to androgens influences morphology and aggressive behavior of male and female mice. Hormones and Behavior, 1979, 12, 1-11.


vom Saal, F. S. Variations in endocrine and parental behavior in male mice due to prior androgenic exposure to female females. Eliminations by prenatal stress. Physiology and Behavior, in press. (a)

vom Saal, F. Sex differences in behavior and population dynamics in mice. In R. Blasschak, C. Blanchard & K. Flennager (Eds.), Biological parameters on aggression. New York, Lit, in press. (b)

vom Saal, F. P. The interaction of circulating androgens and estrogens in regulating mammalian sexual differentiation. In J. Balthazer, E. Price & G. Jones (Eds.), Hormones and behavior in the male. Berlin: Springer-Verlag, in press. (c)

vom Saal, F. Preovulatory and ultrasonic causes of infanticide in male house mice. In C. G. Haufler, S. Blaffer-Herz & C. Vogel (Eds.), Infanticide in animals and man. Springer-Verlag, in press. (d)


vom Saal, F. S. & Bronson, F. H. Sexual characteristics of adult female mice are correlated with their blood concentration levels during prenatal development. Science, 1980, 209, 397-399. (a)


vom Saal, F. S., Grant, W., McMillen, C., & Lawe, K. High fetal estrogen levels correlate with enhanced adult sexual performance and decreased aggression in male mice. Science, in press.