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# PERINATAL TESTOSTERONE EXPOSURE HAS OPPOSITE EFFECTS ON ADULT INTERMALE AGGRESSION AND INFANTICIDE IN MICE

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## INTRODUCTION

In this chapter findings with house mice (now classified as Mus domesticus rather than Mus musculus[1]) concerning the effects of sex steroid exposure during the perinatal period of sexual differentiation on adult infanticidal behaviour and intermale aggressive behaviour are reviewed. The perinatal period of sexual differentiation in mice begins with testicular differentiation on about Day 12 of foetal life (pregnancy typically lasts 18-19 days in mice) and continues through the first week of postnatal life[2]. During this time sex steroids influence the structure and function of numerous organs, including the brain and thus behaviour.

Most studies of early hormonal effects on behaviour have concerned the ontogeny of copulatory behaviour, while fewer studies have addressed the role of sex steroid exposure during perinatal life on other activities, such as infanticide, intrasex aggression, postpartum aggression, social interactions and learning[3-6]. The effects of sex

steroid exposure during early life on the above behaviours are not always what one would predict on the basis of studies of copulatory behaviour[2,7]. Specifically, experiments will be described demonstrating that during the perinatal period of sexual differentiation, testosterone (T) influences the likelihood of animals engaging in intermale aggression and infanticide in adulthood. But the effects of perinatal T exposure on these two types of aggressive behaviour are always opposite.

## THE RELATIONSHIP OF GENOTYPE TO THE FREQUENCY OF INFANTICIDE

Violence exhibited by adults toward preweanling young, (referred to here as "infanticide"), has been documented in most classes of vertebrates[8]. Until recently, infanticide was considered a pathological behaviour, the occurrance of which was due to a breakdown in social structure, such as that observed by Calhoun[9] in freely growing, confined populations of rats when density levels became high. There is now overwhelming evidence that infanticide evolved as one component of the reproductive strategies of both males and females in species with particular reproductive traits (reviewed in[8,10]).

One common procedure used to test mice for the tendency to exhibit infanticide has been to quietly place a newborn mouse pup into a corner of the resident's home cage. An

animal is classified based on its response to the pup during a test that typically lasts about 10-30 minutes (infanticide usually occurs within one minute in such tests). Animals are labelled as infanticidal if the pup is attacked (bitten), and they are labelled as parental if a nest is built, the pup is retrieved to the nest, groomed, and kept warm. In cases where the pup is investigated but not picked up or injured by the resident, the pup is identified as having been "unhandled".

More is known about the variables influencing the exhibition of infanticide in both male and female house mice than in any other species[11-27]. One of the intriguing aspects of this behaviour is that male mice from different genetic stocks differ markedly in the frequency with which infanticide is observed (Figure 1). Using the testing procedure described above, no inbred male AJ mice exhibited infanticide (unpublished observation). AJ mice are an interesting strain in that pregnancy lasts 20-21 days (unpublished observation). In contrast, most C57BL/2J male mice exhibit infanticide[21]. This strain is more typical since pregnancy lasts 18 days.

The significance of length of pregnancy, and thus prenatal T exposure, to the incidence of infanticide ir different mouse stocks will be discussed below. Differences in the frequency of infanticide were also observed in the laboratory-reared offspring of two different stocks of

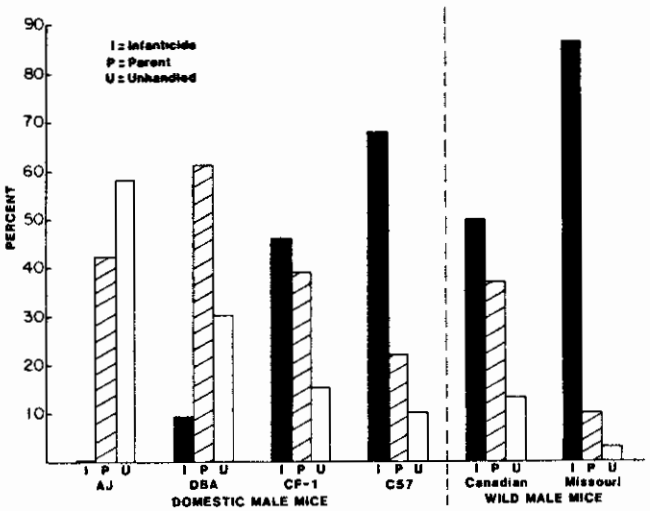


FIGURE 1. The proportion of male mice from different genetic stocks that responded to a newborn mouse pup by either: 1. exhibiting infanticide (biting the pup), 2. behaving parentally (building a nest, retrieving the pup to the nest, grooming the pup, and hovering over the pup to keep it warm), or 3. leaving the pup unhandled during a 15-30 min test in each male's home cage. For domestic stocks, AJ, C57BL/6J and DBA/2J are inbred strains, while CF-1 mice are outbred. The laboratory-reared offspring of two stocks of mice trapped in either Columbia, Missouri or Alberta, Canada were also tested (unpublished observation; [19,21]).

wild-trapped mice: one stock was trapped in Alberta, Canada, and the other stock was trapped in Columbia, Missouri.

In the CF-1 stock used in many of the studies described here, infanticide is sexually dimorphic: few females spontaneously kill pups while about 45% of males kill pups. In wild stocks of mice, however, the likelihood of females exhibiting infanticide is much higher than any examined domestic stock[15,16,28]. The infanticidal tendency also varies

as a function of reproductive state in wild female mice[17,20]. The role of hormones in the regulation of infanticide in adult wild female mice, as well as the basis of individual differences in the behaviour of adult females toward young, is currently under investigation.

## THE RELATIONSHIP OF PERINATAL TESTOSTERONE TO ADULT INTERMALE AGGRESSION AND INFANTICIDE

Initial experiments concerning effects of exposure to T during perinatal development in rodents focused on the sterilizing action of this hormone on females shortly after birth (T-treated females are unable to ovulate[29]). Such treatment also increases aggression towards male opponents (referred to as intermale aggression) and masculine sexual behaviour toward a receptive female[5,6,29,30]. The conclusion from these studies was that T masculinized and defeminized the brain in terms of behaviour and neuroendocrine function.

The period of maximal sensitivity to the permanent effects of T was later extended to include the prenatal stage of sexual differentiation. For example, exogenous administration of testosterone propionate (TP) to pregnant female mice increases masculine behaviour (such as aggression toward a novel male) in female offspring; there is not an enhancing, or supermale, effect on male offspring[5]. In summary, there are permanent enhancing effects on adult aggressive behaviours due to exposure to T throughout the

perinatal period of sexual differentiation in mice[4,6].

For an adult male or female mouse to exhibit intermale aggression when confronted by an adult male, blood levels of T must be above threshold values[6]. When an adult female mouse is induced by prolonged treatment with T to attack a male, this behaviour is referred to as intermale aggression. Aggression toward an adult male would not typically be exhibited by a female except while nursing young (interfemale aggression does occur between nonlactating females, and exogenous treatment with T is not required for this behaviour[2,7]). In domestic (but not wild) female mice, adult treatment with T is also required to induce infanticide[23,31]. Thus, both intermale aggression and infanticide are male-typical behaviours that can be activated in adult female mice from domestic stocks by treatment with T.

The relationship between exposure to T during perinatal life and the tendency to exhibit both intermale aggression and infanticide in adulthood was investigated in male and female Rockland-Swiss (R-S) mice. In these studies most males and females were gonadectomized within 12 hr of birth and either injected with TP dissolved in oil or the same volume of oil as a control. One group of males was castrated 10 days after birth and thus exposed to T produced endogenously (rather than by injection after castration) during early postnatal life. In adulthood all the above animals received

subcutaneously implanted silastic capsules containing T; the animals were then tested every few days in their home cages for their behaviour toward either a newborn pup or an adult male that had had its olfactory bulbs removed (bulbectomized animals elicit attack but do not reciprocate when attacked).

The findings presented in Figure 2 clearly demonstrate that female mice that are gonadectomized on the day of birth and given only oil do not respond to adult treatment with T by attacking a male placed into their cage during a 10-day treatment period. These females will eventually become aggressive, but a prolonged period (about 3 weeks) of exposure to T is required[5,6]. In contrast, this same treatment leads to virtually all females exhibiting infanticide when exposed to a newborn pup[32]. Treatment of females with TP on the day of birth greatly increases the likelihood that attack toward an adult male intruder will be observed[5], while the frequency of infanticide is dramatically reduced[32].

The same relationship was observed in males exposed to elevated levels of T during early postnatal life, namely, an increased frequency of intermale aggression and a decreased frequency of infanticide[5,32]. The lower frequency of infanticide and higher frequency of intermale aggression in males relative to females (Figure 2) for the animals castrated at birth and injected with oil can be accounted for

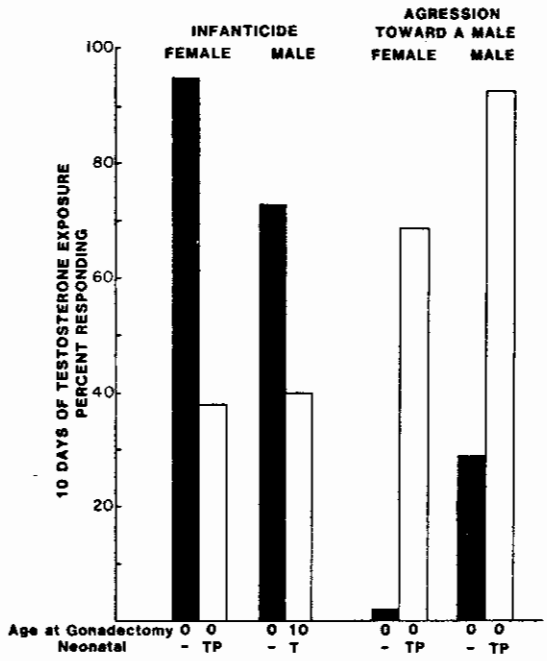


FIGURE 2. The percent of Rockland-Swiss mice responding to the presence of a newborn pup by exhibiting infanticide or to the presence of an adult male by exhibiting aggression within 10 days of being implanted in adulthood with a silastic capsule containing testosterone (T). Animals had been castrated on the Day of birth (Age of gonadectomy = 0) and immediately injected with either testosterone propionate (TP) dissolved in oil or just oil ("-" = oil injection). One group of males was gonadectomized at 10 days of age; these males were exposed to T produced by their own testes during early postnatal life[5,32].

by males being exposed to higher circulating titres of T than females throughout the last third of gestation[7,33,34].

The possible role of intracellular enzymes that amplify the effects of T by conversion to more potent hormones has been examined [5$\alpha$-reductase metabolizes T to dihydrotestosterone (DHT), which then binds to intracellular androgen receptors, while aromatase metabolizes T to

oestradiol ($E_2$), which then binds to intracellular oestrogen receptors]. The inhibiting effect on adult infanticidal behaviour typically observed in animals treated with TP on the day of birth was also observed in R-S mice treated neonatally with oestradiol benzoate (EB). Since the dose of EB administered (40ug) was quite high, the possibility that this is a nonspecific response to a pharmacological dose of a steroid cannot be ruled out. However, neonatal treatment with the antioestrogen, MER-25, concurrent with TP treatment, blocked the inhibiting effect of neonatal TP exposure on adult infanticidal behaviour. In contrast, neonatal treatment with the long-acting (propionate) form of the reduced metabolite of T, DHT-propionate, did not inhibit adult infanticidal behaviour[27].

Neonatal treatment with EB enhanced intermale aggression in mice, similar to neonatal treatment with TP, although again, a very high dose of EB (50ug) was used in this study[35]. Taken together, these findings support the hypothesis that the effects of neonatal T exposure on adult intermale aggression and infanticidal behaviour requires aromatization of T to E within the neural substrates mediating these behaviours. It has also been well documented that intracellular aromatization of T to $E_2$ during perinatal life mediates masculinization of the neural substrate mediating male copulatory behaviour and defeminization of the

capacity to exhibit a preovulatory surge in LH[29].

## Intrauterine Position of Foetuses Influences Adult Intermale Aggression and Infanticide

In this section the relationship of individual differences in circulating levels of T during foetal life and the tendency to exhibit both intermale aggression and infanticide in adulthood is discussed. A naturally-occurring developmental event, referred to as the "intrauterine position phenomenon"[36] (see Figure 3), has provided a valuable model for studying relationships between foetal hormone levels and adult behaviour and physiology without pharmacological intervention. Implantation of male and female embryos at any position in the uterus is a random event[36]. Again, male foetuses secrete higher titres of T during the last third of gestation than do females. Male foetuses situated within a uterine horn between 2 male foetuses (2M males) have higher circulating titres of T than counterparts situated between female foetuses (0M males); 1M males are situated between a male and a female foetus and are intermediate between 0M and 2M in their blood T levels (Figure 4; unpublished observation).

The relationship between serum T levels during foetal life and adult behaviour toward a newborn pup placed into the home cage was examined in 0M, 1M and 2M CF-1 male mice. The mice examined for their behaviour were delivered by Cesarean

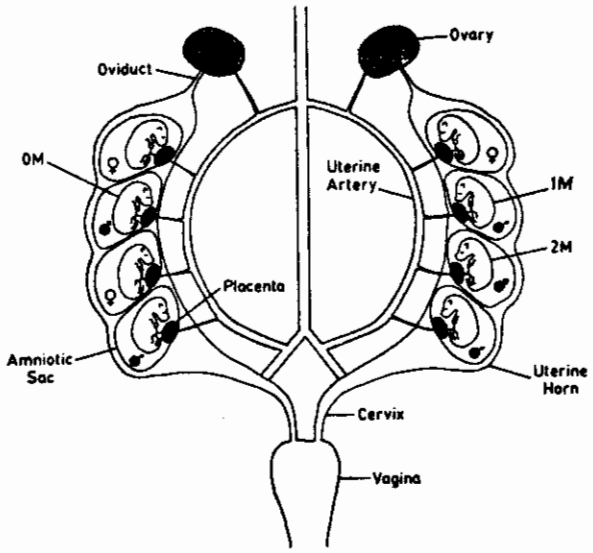


FIGURE 3. Schematic diagram of the uterine horns and uterine loop arteries of a pregnant mouse at term. Mice are time mated, and just before parturition the foetuses are removed surgically and raised by foster mothers; blood is collected from other foetuses at various times during pregnancy. The intrauterine position of each male foetus is determined by the sex of contiguous foetuses: 2M = between 2 males, 1M = between a male and a female, 0M = between 2 females[36].

section, their intrauterine positions were recorded, and they were raised by foster mothers; foetal blood was collected from animals different from those tested for their behaviour. About 45% of adult, virgin CF-1 male mice exhibit infanticide[19,25,26] (Figure 1). During foetal life, 2M males have higher circulating titres of T than 0M males, and in adulthood most 0M males exhibit infanticide while most 2M males behave parentally; 1M males represent 50% of the male population[36], and they are equally likely to exhibit infanticide or parental behaviour[23] (Figure 4). It thus

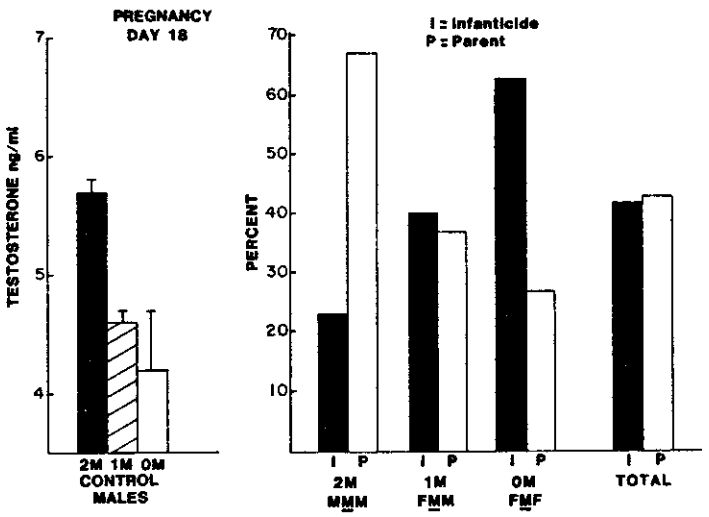


FIGURE 4. The serum levels of testosterone (measured by radioimmunoassay) on Day 18 of foetal life (Day 0 = mating) in 0M, 1M and 2M CF-1 males (ANOVA; $p < .05$; unpublished observation). The proportion of adult 0M, 1M and 2M CF-1 male mice exhibiting infanticide (I) or parental behaviour (P) in response to the presence of a newborn pup placed into their home cage[23].

appears that variation in gonadal steroid concentrations (0M and 2M males also differ in their exposure to oestradiol[34]) during foetal life due to the intrauterine position phenomenon is one factor influencing individual differences in behaviour in male mice.

Intermale aggression was examined in 0M and 2M CF-1 male mice that were castrated at the time of Cesarean delivery to eliminate any postnatal differences in exposure to gonadal hormones. These animals were implanted with silastic capsules containing T and tested in their home cages for aggression against an olfactory-bulbectomized male every other day as

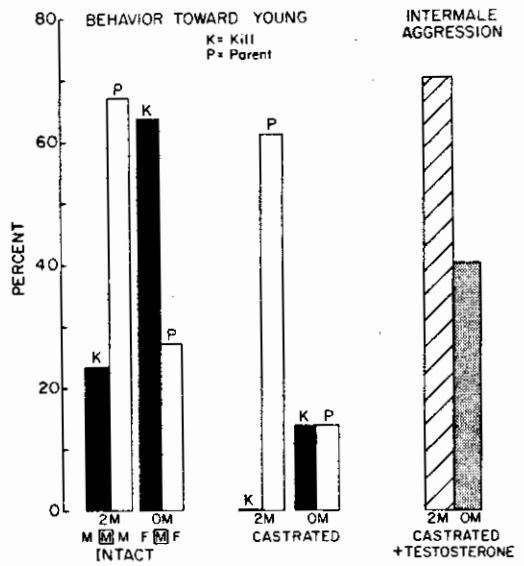


FIGURE 5. The behaviour of adult 0M and 2M male CF-1 mice that were gonadally intact or castrated at 28 days of age toward a newborn pup placed into their home cage (K = kill, P = parental; the percent leaving the pup unhandled is not shown). Castrated animals were not treated with testosterone[23]. The proportion of 0M and 2M male CF-1 mice (castrated at birth) that attacked a male opponent within 16 days after being implanted with a silastic capsule containing testosterone in adulthood[34].

described above (see Figure 2). The data presented in Figure 5 reveal that more 2M than 0M males exhibited intermale aggression within 16 days of exposure to T[34]. The studies using males from known intrauterine positions thus reveal the same negative relationship between the propensities for intermale aggression and infanticide described in Figure 2: the perinatal hormonal environment that increases the likelihood of animals exhibiting intermale aggression (elevated levels of T) reduces the likelihood of animals exhibiting infanticide in adulthood.

Adult Activation vs. Perinatal Sensitization, Desensitization and Organization of Behaviours by Gonadal Steroids

Activation. A model describing the relationship of high vs low blood levels of T during the perinatal period of sexual differentiation and the likelihood of exhibiting either intermale aggression or infanticide in adulthood is presented in Figure 6. Adult T exposure is said to activate the neural substrates for these behaviours, even though the specific sites at which T might be acting within the brain have not been elucidated. In response to the appropriate stimulus (an unfamiliar male mouse), aggression will be observed in previously castrated mice after only a very short activational period of exposure to T if prior sensitization has occurred.

Sensitization. The capacity for T to activate a particular neural substrate depends on the levels of T to which individual mice were exposed during early life. In the case of intermale aggression, the higher the circulating titres of T (within a specified range) during early (perinatal) life, the shorter the required time interval after the initiation of exposure to T in adulthood before a gonadectomized male mouse responds to the presence of a novel male by exhibiting aggression[6]. During early life T thus sensitizes the neural substrate mediating intermale aggression to the later (adult) activational effects of T on this neural substrate.

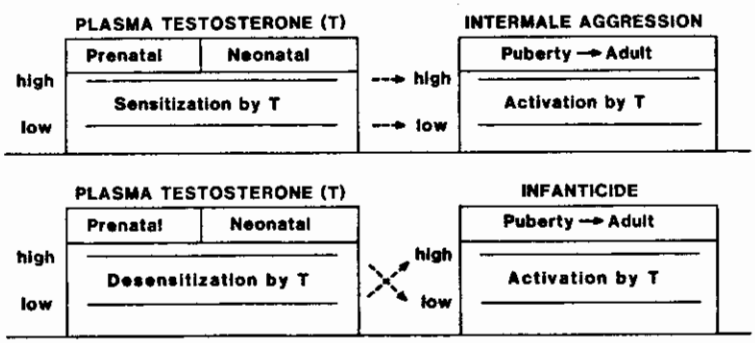


FIGURE 6. Schematic diagram depicting the effect in mice of exposure to high vs. low titres of T during perinatal (prenatal and neonatal) life. High levels of T during perinatal life sensitize the neural substrate mediating intermale aggression and lead to high aggressiveness in adulthood, but only if T is present to activate the neural substrate mediating aggression. In contrast, high levels of T during perinatal life desensitize the neural substrate mediating infanticide to later activation by T such that most animals behave parentally toward pups in adulthood.

There are clear sex differences in both brain structure and function in most species that have been examined, including mice[37]. These differences are not reflected by the inability of gonadectomized male or female mice (regardless of their perinatal hormone levels) to respond to the activational effects of T on intermale aggression. Even without prior sensitization during perinatal life, intermale aggression eventually occurs after adult treatment with T, although the time required for activation to occur can be quite long: about 3 weeks in most female mice as well as most males that were exposed to an antiandrogen throughout the

perinatal period[5,6,38].

Desensitization. The effects of T during perinatal life on the neural areas mediating infanticide provide a direct contrast to the sensitizing effect of T on the neural substrate mediating intermale aggression. The neural areas mediating infanticide respond to an elevation in T during perinatal life by becoming desensitized to subsequent activation by T in adulthood. The result is that while perinatal exposure to elevated levels of T increases the response to T in adulthood in terms of attacking an adult male, it decreases the likelihood that infanticide will be observed.

Organization. The essential role played by T in activating infanticide in domestic mice has been previously described. Castration abolishes infanticide in virtually all males. When 0M and 2M male mice were castrated when 28 days old and were then tested at 2.5 months of age for their behaviour toward young without being treated with T, only a few (14%) 0M males and no 2M males exhibited infanticide. In gonadally-intact males, most 0M males but few 2M males kill pups (Figure 4). In contrast, 0M and 2M males still differed markedly in parental behaviour 50 days after castration: most (61%) castrated 2M males, but only a few (14%) 0M males, exhibited parental behaviour. This is similar to intact males from the same intrauterine positions[23] (Figure 5). This suggests that

during early life, the brain of a 2M male is organized such that when he comes in contact with pups, parental behaviour is exhibited regardless of whether he is gonadally intact.

When a behaviour is influenced by a hormone during early life, but the presence of a specific hormone is not required for it to be exhibited during later life, the behaviour is described as having been organized. One of the best known examples of behavioural organization is the exhibition of sex differences in play behaviour in infant rhesus monkeys that are gonadectomized at birth[39]. This is in contrast to other behaviours, such as copulation, intermale aggression or infanticide in house mice, where adult activation by T is required to observe differences due to perinatal T exposure.

One final point concerning the requirement for hormonal activation of behaviours is that this is only true of naive animals. In general, the more experience an animal has exhibiting a behaviour (such as fighting or copulation), the longer it will be exhibited after removal of the activating hormone. This does not mean that the behaviour has become organized by experience, since the likelihood of observing the behaviour decreases as a function of time after castration. In contrast, organized behaviours do not exhibit this decay with time.

As described above, the effects of early hormone exposure may bias the outcome of the fights between <u>naive</u>

males (2M males may be the most likely to become dominant). As a result of fighting, however, the effects of early hormone exposure become dissociated from aggressiveness; it is the outcome of these fights that actually determines the subsequent degree of aggressiveness of each male. Dominance status also influences other behaviors. For example, dominance status was established by pairing CF-1 male mice for seven days. Subordination inhibited infanticide in CF-1 male mice while winning fights and becoming dominant caused most of the males that did not exhibit infanticide prior to fighting to become infanticidal[26] (Figure 7). Dominant and subordinant males were also placed with three sexually-receptive females. The subordinate males inseminated fewer females than did the dominant males (unpublished observation).

Prenatal Testosterone Exposure and Strain Differences in the Frequency of Infanticide

The data presented in Figure 4 reveal a significant correlation between plasma T concentrations during foetal life and adult infanticidal and parental behaviour in 0M, 1M and 2M male CF-1 mice. Svare and colleagues proposed that strain differences in the frequency of infanticide among male mice, such as depicted in Figure 1, could be due to strain differences in the perinatal hormonal environment[16,21]. For example, male foetuses carried by wild mice trapped in

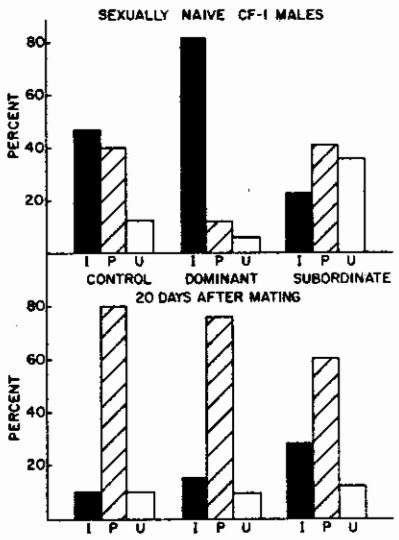


FIGURE 7. The effect of winning (dominant) and losing (subordinate) fights on the behaviour of adult male CF-1 mice toward young: I = infanticide, P = parental, U = unhandled. Fighting occurred on the 7 days prior to the test for infanticide. Control males were individually housed throughout the experiment. Males were sexually naive at the time of testing for infanticide or had been mated 20 days prior to the test; they were thus tested when their own young would have just been born[26].

Missouri had only about 50% of the plasma T concentrations of CF-1 male foetuses at the same time in fetal life[19]. Since there is a correlation between high levels of T during early life and a low frequency of infanticide in adulthood, it is possible that wild male mice are more likely than CF-1 males to exhibit infanticide due to their lower levels of T during early life.

Another possible factor in mediating strain differences in infanticide is the length of pregnancy. In mice, the placentae are the major source of androgen secretion during

pregnancy[40,41]. Mice do not appear to have a sex steroid binding globulin (found in many other mammals) that serves to bind circulating T, thus restricting the passage of T from the blood into cells[42]. Mice that have a prolonged pregnancy (such as the AJ strain mentioned earlier) have the longest exposure to supplemental T of placental origin and are also the least likely to exhibit infanticide in adulthood. In contrast, mice with an 18-day pregnancy (wild mice, C57 mice) are the most likely to exhibit infanticide in adulthood. CF-1 mice have a 19-day pregnancy and are intermediate between wild mice and AJ mice in the likelihood that males will exhibit infanticide in adulthood (Figure 1).

## ECOLOGICAL AND EVOLUTIONARY CONSIDERATIONS

A final question is whether the negative correlation between infanticide and intermale aggression in male house mice evolved because it is adaptive to have the male that is most likely to exhibit aggression when confronted with a strange male be the least likely to kill infants. The idealized mouse breeding unit (deme) may be described as consisting of a single dominant male siring almost all young, a few subordinant males that do not sire young, and a number of females (some of which will be pregnant or nursing). This type of social structure is commonly observed in the laboratory when mice are placed into areas large enough to

allow partitioning into territories. Demes are also considered typical of mice living as commensals of man[43].

Subordinant male mice may be tolerated within a deme since subordination inhibits infanticide (Figure 7). Subordinate males are thus not a threat to the offspring produced by the dominant male while the dominant male is alive. If the dominant male in a deme dies, subordinant males fight until one becomes dominant. The sexual-competition hypothesis[10,18,24,26] predicts that this new dominant male should kill the nursing offspring of the prior male to release the females from the lactational suppression of ovulation; the females would then rapidly ovulate and mate with the new dominant male. In experiments to test this hypothesis conducted with both CF-1 mice[26] and the offspring of wild mice trapped in Missouri[18], infanticidal males produced young more rapidly than noninfanticidal males whether infanticide occurred before[26] or after[18] postpartum oestrus. This finding suggests that if infanticide has a genetic component (an assumption of the sexual-competition hypothesis), genes influencing infanticide should rapidly increase in frequency in the population.

The possibility of a net decrease in fitness due to killing related young also has to be considered. If the new dominant male has remained in his natal deme and is confronted with pups with a high coefficient of relatedness,

exhibiting infanticide might not be the strategy that optimizes reproductive success. It is possible that males with the highest likelihood of remaining in their natal environment and becoming dominant are 2M males, which are the most likely to be aggressive toward other adult males but the least likely to exhibit infanticide. It follows that the males that fail to become the dominant male in the natal environment may have a prenatal bias toward lower intermale aggressiveness, perhaps due to exposure to lower levels of T during early life (such as 0M males); these males should be the most likely to exhibit infanticide, since any lactating females and their pups encountered after dispersing from their natal deme are unlikely to be related.

The act of mating (specifically, ejaculating[25]) inhibits infanticide in male CF-1 mice[26] (Figure 7) and wild mice[18]. This inhibition only occurs from shortly before the birth of a male's own young to the time that they would normally be weaned (between about 2 weeks to 7 weeks after mating, at which time a male's offspring would be about 30 days old[25]). The mechanisms mediating this time-contingent inhibition of infanticide and stimulation of parental behaviour in male mice is under investigation, but this may be an evolved strategy which guarantees that a male mouse will not exhibit infanticide at times during which his own young could be killed.

## CONCLUSION

All the experimental and correlative studies with mice described here suggest that the hormonal condition during perinatal life that increases the likelihood of exhibiting intermale aggression (high T levels) also decreases the likelihood of exhibiting infanticide. The prediction of a negative correlation between intermale aggression and infanticide in terms of reproductive success in natural populations is highly speculative. One can probably find a population of mice with almost any kind of social structure, since house mice are opportunists that have been extremely successful at exploiting a wide variety of ecological niches[43]. This raises a question as to whether one can reasonably speculate about the evolution of behaviour in mice in relation to a specific social structure. The value of the proposed hypothesis, however, is that some aspects can be directly tested. For example, mice can be allowed to establish demes in seminatural environments. Animals from known intrauterine positions can be fostered to female inhabitants at the time of normal parturition (the female's own young would be removed). The likelihood of 0M, 1M or 2M male offspring becoming the dominant male (if the prior dominant male is removed or additional territory is provided) can be determined. The experiment can be designed with

pregnant and lactating females present to determine whether the predicted correlation with the tendency to exhibit infanticide is observed.

One of the goals of aggression research has been to provide information concerning the relationship between different behaviours that are categorized as aggression. This has proven a difficult task to accomplish. The present focus has been on laboratory experiments documenting a significant negative correlation for two such behaviours: intermale aggression and infanticide. Future research concerning the proximate (hormonal, experiential) factors mediating infanticide, intermale aggression and other behaviors in mice needs to be designed with relevance to reproductive success of individuals in natural populations. Integrating findings and research strategies from ecological studies of natural populations of mice and laboratory experiments will provide valuable insights that could not be achieved without an appreciation of the value of information gained from both disciplines.

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