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Time and Sex in the Male Mouse: Temporal Regulation of Infanticide and Parental Behavior

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Summary: Infanticide is a violent but successful reproductive strategy found in many mammals, particularly rodents. In male house mice (*Mus domesticus* and *M. musculus*), the act of ejaculation provides a reliable neural signal for timing the birth of their offspring. However, a unique chronobiological aspect of this phenomenon is the extraordinary temporal latency that can occur between the stimulus (coital ejaculation) and its adaptive neural response (male mice cease killing pups and behave parentally toward them instead). Specifically, the inhibition of infanticide is often time delayed for many days after a male ejaculates, but virtually always occurs before or around the time his own sired offspring would be born 18–20 days later. Furthermore, infanticide spontaneously reemerges 50–60 days after mating. In CF-1 stock male mice this entire behavioral sequence is synchronized with the female's reproductive cycle, and occurs even in the total absence of social cues or changes in pituitary or gonadal hormones after mating. When entrained and mated at 22 h (light:dark 11:11) or 27 h (light:dark 13.5:13.5) T-cycles, photoperiodic cues appeared to synchronize this dramatic shift in behavior, because a sudden transition from pup killing to parenting was matched with the number of light/dark cycles experienced after ejaculation rather than the amount of real time experienced, suggesting a circadian timing link. Housing in constant light accelerated the postmating transition to parenting, whereas constant dark significantly delayed the transition to parenting, but still occurred by 3 weeks after mating. Most males tend to oscillate between infanticide and parental behavior for several days before locking in to constant parenting, regardless of lighting conditions. Variation in the time delay between ejaculation and the inhibition of infanticide was consistent within young individuals (<10 months of age), but in older males (>18 months of age) the time interval between ejaculation and parenting was significantly prolonged and attenuated. Another unique aspect of this phenomenon is that variation among individuals in their timing and response to light cues is correlated with phenotypic variation in sex steroid exposure during late fetal development. So far, no simple physiological explanation can account

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for the neural mechanism triggered by ejaculation that coordinates these time-delayed behavioral changes toward pups. **Key Words:** Infanticide—Parental—Ejaculation—Fetal position—House mouse—*Mus*—Light/dark cycle—Aging—Circadian—T-cycle.

Infanticide—defined as the killing of conspecific young—is no longer considered maladaptive or sociopathological. It occurs in a wide variety of organisms of both sexes (1–4) and, in most natural situations, infanticide represents a violent but extremely effective reproductive strategy. With regard to male mammals, for example, field and laboratory studies have dramatically documented the reproductive advantages that accrue when an infant-killing male usurps the territory of another male. By killing the offspring of a defeated competitor, an infanticidal male benefits in two ways: first, he eliminates potential genetic and resource competition with his own offspring, and second, once a female's own young are killed, she rapidly ovulates again, typically being remated by the usurper male.

Infanticide is ubiquitous among rodents (5). When a male house mouse (*Mus domesticus* or *M. musculus*) encounters a neonate, he either tries to kill it or he does not harm it. Obviously, an effective infanticidal strategy must provide behavioral mechanisms that prevent male mice from accidentally killing their own progeny. Social cues, fetal and adult hormones, and genetic differences are three factors known to modulate a male's behavior toward pups (6–9). However, there is a fourth and physiologically unique dimension to infanticide: time-dependent changes in a male's behavior toward pups are triggered specifically by the stimulus of ejaculation during mating (10–12).

A UNIQUE TIMING PHENOMENON

It is now extensively documented that male house mice can use the stimulus of coital ejaculation as a reliable neural signal for timing the birth of their offspring (9,10). Ejaculation inhibits infanticide; however, a remarkable aspect of this phenomenon is that a male's pup-killing behavior often does not cease for many days after mating, but nearly always ceases by the time his own sired offspring would be born 3 weeks later. When infanticide ceases, males routinely express parental behavior toward pups similar to that of a newly lactating female. Furthermore, infanticidal behavior spontaneously reemerges after offspring are weaned (10). These timed behavioral changes, which result specifically from coital ejaculation, occur consistently among various house mouse stocks (7–9,13,14). This phenomenon also occurs in the Norway rat, *Rattus norvegicus* (15), and probably in other rodents as well.

CF-1 stock male mice (*Mus domesticus*) are a superb model for studying the behavioral events triggered by ejaculation. There are four distinct phases to the CF-1 male's behavioral cycle toward pups: (a) In virgin males, ~50% of all individuals spontaneously kill pups, whereas the other 50% parent them; (b) ejaculation intensifies pup-killing behavior such that virtually all males will attack and kill pups during part or most of their mate's pregnancy; (c) by the time pups are born 18–20 days later, infanticide ceases and males behave parentally during their mate's lactation; (d) the

reemergence of infanticide occurs between 50 and 60 days after mating and coincides with weaning. Remarkably, this entire behavioral cycle occurs even when a CF-1 male is kept totally isolated from his mate and deprived of any social cues after copulation (10,11). We are unaware of any other similar neural phenomenon evolved in mammals where such dramatic shifts in adaptive behavior are timed to occur so many days—indeed weeks—after a specific stimulus such as ejaculation.

The remainder of this article briefly reviews our preliminary findings about the nature of the ejaculatory trigger and the resulting time-delayed behavioral changes in CF-1 males. We have monitored the timing of pup-killing and parenting strategies when males were housed and mated at various light/dark regimens, including free-running rhythm conditions of constant light and constant dark. We have also correlated individual variation in the neural timing of these behaviors with hormonal events that occur during late fetal development. Finally, we have examined the effects of both remating and aging on the timing of these strategies. In all, our research has yielded a variety of exciting chronobiological phenomena.

ASSESSING INFANTICIDAL AND PARENTAL BEHAVIOR IN MALE MICE

An infanticidal male mouse will approach a pup, rattle his tail, and suddenly lunge at and attempt to kill the pup with rapid bites to its head and back. In dramatic contrast, a parental male gently retrieves a pup to his nest where he grooms it and keeps it warm. These are clear-cut, unambiguous behaviors. We assess a CF-1 male's behavior by sliding a 1- to 3-day-old newborn inside a 4- to 5-cm tube made of 1.5-mm^2 wire mesh screen; the protected pup is then placed in the male's home cage. When an infanticidal CF-1 male encounters a screen-protected pup, he typically attacks and repeatedly bites at the screen, but without harming the neonate (16). If a male does not show any intent to harm the pup, he is then tested with an unprotected pup in order to verify his parental behavior. Neither the sex, age, nor relatedness of the pup appear to have any discernable influence on a male's tendency to exhibit infanticide or parental behavior. Thus, a male's reaction toward a newborn pup is a generalized, nonspecific response with intravaginal ejaculation serving as the specific neural trigger that initiates the behavioral changes described earlier.

HOW DO MATED MALES KEEP TRACK OF TIME?

The unusually prolonged sequence of behavioral changes triggered by the ejaculation prompted us to ask how males gauge the passage of time after mating. Because CF-1 males exhibit this response in total social isolation, this implied the presence of a unique neural timing system modulating these behaviors. We postulated that mated males could measure time either by (a) assessing the amount of absolute (real) time passing after ejaculation, or (b) assessing the number of light/dark cycles experienced after ejaculation. In natural situations, photoperiodic variation provides infallible temporal entrainment cues, so we suspected the second hypothesis. To test both possibilities, we used an experimental paradigm that allowed us to distinguish between absolute time (as measured in 24-h days) versus the number of light/dark cycles experienced (17).

Fast versus Slow Time

One hundred adult virgin CF-1 males were housed in light-tight boxes illuminated inside with a 15-W fluorescent lamp (initial light:dark cycle 12 h:12 h). Half were slowly adapted to an artificially Fast (22-h) daylength (light:dark 11:11), whereas the other half were adapted to an artificially Slow (27-h) daylength (light:dark 13.5:13.5). Entrainment to each T-cycle was verified by monitoring the activity patterns of eight sentinel males kept in running wheel cages interfaced to an event recorder. All experimental males were mated with an estrus-primed female at the time of lights on, tested for infanticide, and then retested between 16 and 25 absolute (24-h) days after mating. Specifically, half of the fast day males were retested at 16.3 absolute days (18 light/dark cycles) and half were retested at 20 absolute days (22 light/dark cycles) after mating, whereas half of the slow day males were retested at 20 absolute days (18 light/dark cycles) and half were retested at 24.8 absolute days (22 light/dark cycles) after mating. Because CF-1 pups are born 19 days after mating, our experimental objective was to bracket the time when pups are born by comparing both groups directly at 20 absolute days after mating, while also controlling for the same number of light/dark cycles experienced (18 vs. 22 cycles). The rationale behind this paradigm is visualized in the upper portion of Fig. 1.

The lower portion of Fig. 1 shows the postmating inhibition of infanticide graphed in two complementary perspectives: first, in relation to the number of absolute (24-h) days experienced after mating, and second, in relation to the number of light/dark cycles experienced after mating. At 20 absolute days after mating there was a significant difference in the proportion of infanticidal males in the fast versus slow day groups (13% vs. 61% infanticidal, respectively; $p < 0.005$). In sharp contrast, there was no difference in the proportion of infanticidal males when both groups were matched for experiencing the same number of light/dark cycles. Viewed side-by-side, the graphs in Fig. 1 suggest that photoperiodic cues synchronized the dramatic shift in behavior, because the transition from pup-killing to parenting matched the number of light/dark cycles experienced after ejaculation rather than the amount of absolute time experienced [7].

How Does the Neural Timing System Operate in the Presence or Absence of Photoperiodic Cues?

The results reported here suggest that coital ejaculation triggers a neural timing system that counts photocycles (18), which in turn suggests a circadian link to the timing of these behavioral changes. In the following experiment (11), virgin male CF-1 mice (6 months of age and housed at light:dark 12 h:12 h since birth) were distributed among three animal rooms (n = 30 per group) and maintained at one of three lighting conditions: constant light (LL), light:dark 12 h:12 h (L:D 12:12), or constant darkness (DD). A fluorescent light provided 20–30 lux illumination in the LL and LD 12:12 rooms. After 3 weeks of accommodation, each male was mated with an estrous female, immediately tested with a pup, and then retested every 3 days thereafter until 30 days after mating, with two more retests occurring at 60 and 90 days after mating. All mating and testing was performed at the time of lights on in the L:D 12:12 treatment (2:00 h real time) and all DD observations were accomplished

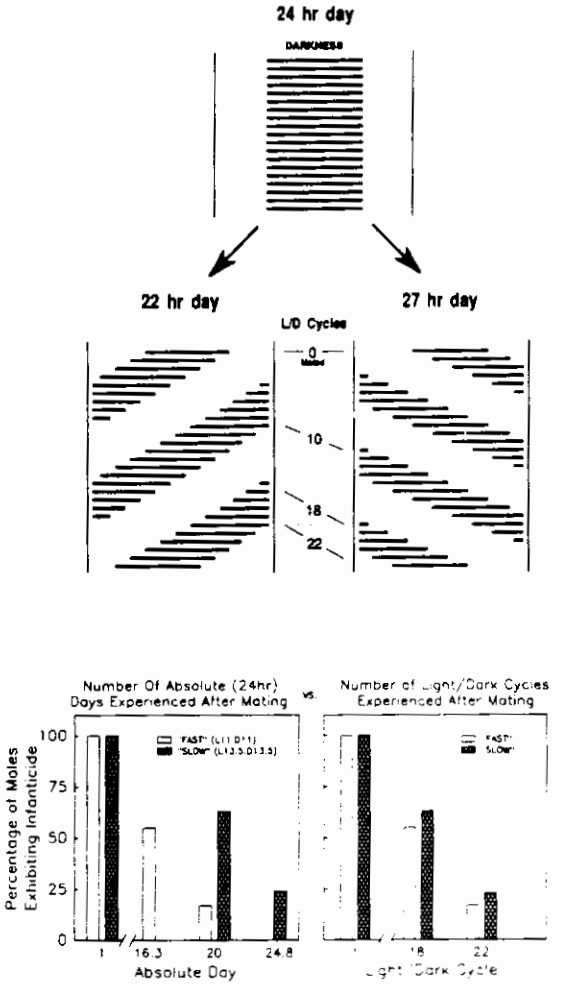

FIG. 1. The upper graphs represent typical locomotor activity patterns generated by male mice kept in running wheel cages at a standard 24-h day (light:dark 12:12) and then entrained to either a 22-h fast day (light:dark 11:11) or 27-h slow day (light:dark 13.5:13.5) T-cycle. The light/dark cycle scale between them illustrates the relationship between absolute (real) time and the increasing divergence in the number of light/dark cycles experienced after mating. Fast-day males were retested for infanticide at 16.3 absolute days (18 light/dark cycles) and 20 absolute days (22 light/dark cycles) after mating, whereas slow-day males were retested at 20 absolute days (18 light/dark cycles) and 24.8 absolute days (22 light/dark cycles) after mating. CF-1 pups are born 19 days after mating, and the dotted line shows the testing match when both groups had experienced 20 absolute days (real time) after mating (see text). The lower graph shows the percentage of fast- and slow-day male mice exhibiting infanticide when the data are graphed in relation to absolute time versus the number of light/dark cycles experienced after ejaculation.

with a 15-W safe red light that remained on continuously in all three rooms. Our purpose here was to see whether mated males would exhibit an appropriate timing pattern in the absence of entraining light/dark cues and, if so, whether males kept in different free-run conditions—and therefore expected to exhibit different circadian periods (Aschoff's rule; see 19,20)—would undergo the transition from pup-killing to parenting at different times after mating.

As shown in Fig. 2, all three groups displayed a temporal pattern of behavioral changes well synchronized with the reproductive cycle of a female mouse. Almost all males were infanticidal immediately after ejaculation; however, the time interval between mating and parenting was significantly prolonged in DD males when compared with their LL and L:D 12:12 counterparts. Significant differences ($p \leq 0.05$) in the frequency of infanticide between DD males and other groups occurred during the first 15 days after mating, but disappeared by the time pups were born. Differences

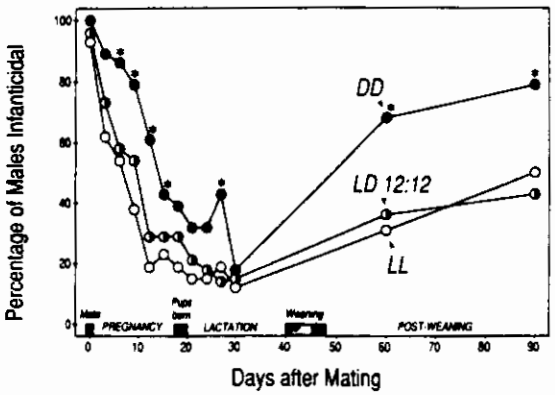

FIG. 2. The time course of infanticide as measured immediately after ejaculation (day 0) until 90 days after mating among CF-1 males housed at various lighting regimens. Asterisks indicate a significant difference ($p \leq 0.5$) between DD males versus their LL and light:dark 12:12 counterparts. No retests were done between 30 and 60 days after mating because previous experiments showed that if males are allowed to interact parentally with a pup during this critical experiential window, most males will continue to exhibit parental behavior for another month or so (10).

reemerged at 27, 60, and 90 days after mating; in fact, nearly 80% of the DD males became infanticidal again after pups were weaned, whereas only 40–50% of the LL and LD 12:12 males did so.

Eight to 10 representative LL and DD males were also monitored in running wheels to see whether any correlation existed between the period of an individual's free-run (as measured by activity onsets) and the timing of postmating behavioral changes (11). Our results were consistent with Aschoff's rule; thus, the circadian activity cycle of DD males ($\tau = 24.1 \pm 0.1$ h) was ~1 h shorter than the cycle of LL males ($\tau = 25.2 \pm 0.2$ h; $p < 0.0001$). Within the LL males, however, there was a significant positive correlation between τ and the number of days elapsed between mating and the expression of parental behavior ($r^2 = 0.75$, $p < 0.05$). In contrast, no such correlation existed in DD animals ($r^2 = 0.16$, $p > 0.25$).

A Circadian Paradox?

As to how this behavioral transition is neurally timed remains perplexing. The results from Fig. 1, where mated males were compared at 22-h versus 27-h T-cycles, suggest a circadian-based timing function. However, the results presented here seem inconsistent with a simple circadian day-counting mechanism. The sample of DD males had an average free-run of ~24 h ($\tau = 24.1$ h), which was the same as the 24-h period of the L:D 12:12 males. Yet, when compared with the L:D 12:12 group, the transition to parental behavior in DD males was significantly delayed, whereas the postweaning reemergence of infanticide was significantly accelerated. In contrast, among LL males, the inhibition of infanticide occurred more rapidly; in fact, the L:D 12:12 and LL groups both showed a similar pattern of temporal changes despite the LL males averaging a 25.2-h free-run. Based on a circadian day-counting hypothesis, one would have predicted that LL males either should have taken longer to undergo the postmating transition to parental behavior or, at the very least, they should not have differed so dramatically from the DD males. However, this experiment still does not allow us to eliminate whether some sort of masking may have occurred, nor do these results completely rule out the unlikely possibility of a covert coordinating rhythm that free-runs independently from activity/rest cycles.

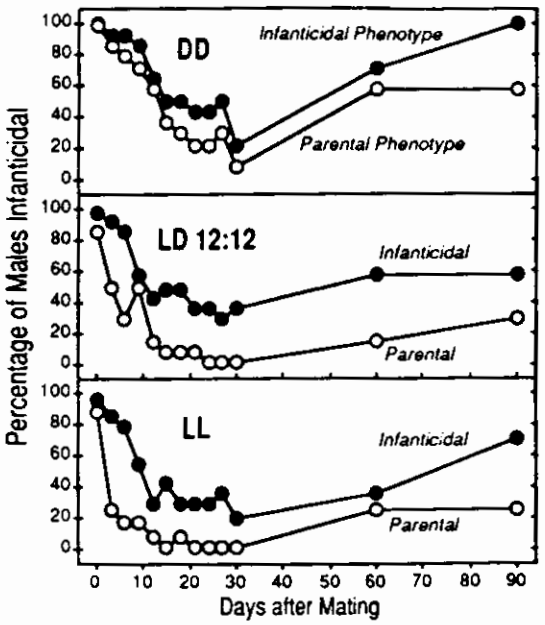

FIG. 3. The temporal pattern of behavioral changes observed when males within each treatment group are graphed in relation to their behavioral phenotype as virgins (infanticidal versus parental), which is correlated with testosterone exposure during late fetal development (see text). Males in each group were ranked according to the day after mating, when they expressed their first bout of parental behavior. Mann–Whitney *U* tests showed significant transition time differences between the two phenotypes in LL ($p < 0.005$) and light:dark 12:12 ($p < 0.005$), whereas in the absence of light (DD), there were no significant differences ($p > 0.40$).

Phenotypic Differences in Response to Light Cues: Fetal Hormonal Programming of Individual Timing Variation

The previous experiment showed another unique aspect of individual timing variation. As noted earlier, we have always found that in any random sample of virgin CF-1 males, ~50% spontaneously kill pups whereas the other 50% exhibit parental behavior (10,11). In mammals such as house mice that produce large litters, fetuses are positioned randomly in the uterine horns. This exposes each fetus to varying sex steroid concentrations depending on whether it develops next to same or opposite sex fetuses (21). As a result, an individual's intrauterine position has been correlated with a profound range of variation among reproductive, morphological, and behavioral characteristics expressed when both sexes are adult, including adult–infant interactions (22). Likewise, past experiments have established that CF-1 males who develop between two male fetuses—and are therefore exposed to higher testosterone concentrations—are significantly more likely to exhibit parental behavior both before and after mating than are males who developed between two female fetuses (12,23–25). Infanticide and intermale aggression are thus inversely correlated in CF-1 males (12,22).

We controlled for this phenotypic variation in fetal hormone exposure by pretesting all virgin males for their behavior toward a pup. Thus, males in each of the three groups of 30 males were allocated such that half were infanticidal and half were parental before mating. With regard to their premating behavior, ejaculation triggered infanticidal behavior in almost all males who were originally parenters and, as shown in Fig. 3, pretested parental males also underwent the postmating transition back to parenting significantly faster than their pretested infanticidal counterparts,

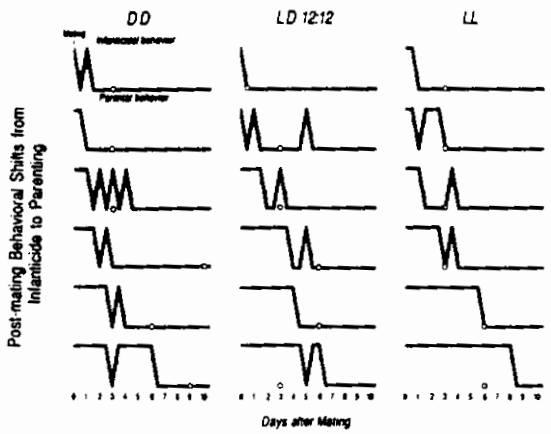

FIG. 4. Day-to-day oscillations in behavior toward pups in individual males (six from each treatment) who were remated at 9 months of age and tested for infanticide every 12 h (each division = 12 h of real time) for 10 days. For comparison purposes, a white dot indicates the day when parental behavior was first noted (as measured at 3-day intervals) when males were mated for the first time at 6 months of age.

but only in the LL and L:D 12:12 conditions. The presence of light in the LL and L:D 12:12 treatments seemed to accelerate the postmating inhibition of infanticide among parental phenotypes, whereas in the DD group there were no significant timing differences between parental or infanticidal phenotypes (11). This intriguing result raises the possibility that variation in timing strategies and differential responses to light cues are programmed hormonally via sex steroids during late fetal development. In a similar vein, we have recently noted differences in the free-run period of house mice derived from different intrauterine positions (G. Perrigo, unpublished observations).

Transition Patterns, Individual Timing Consistency, and the Effects of Aging

In a follow-up experiment, we obtained a more precise picture of the postmating transition pattern of males by assessing their behavior toward pups at much shorter time intervals after mating (every 12 h); we also examined whether variation in time measurement after mating is preserved within an individual (11). Thus, six males from each treatment in the previous experiment who showed relatively rapid transition times from infanticidal to parental behavior after mating were remated at 9 months of age (3 months after their first mating). Unlike their first mating, however, in which retests occurred at 3-day intervals, each retest now occurred every 12 h at the time of lights on (12:00 h) and lights off (24:00 h) in the L:D 12:12 room. Tests in the DD and LL rooms were also conducted at the same absolute time. This resulted in all three groups being tested at either exactly (L:D 12:12) or, because of the free-run in DD and LL males, at ~12-h differences in their circadian phase. It should be explicitly emphasized here that despite the day-by-day phase drift expected among LL and DD males, past experiments have shown that in unmated CF-1 males there are no differences in the frequency of infanticidal and parental behavior, regardless of when they are tested during their circadian phase (11).

As depicted in Fig. 4, a clean transition from pup-killing to parenting behavior sometimes occurred in as little as 12 h, but only in five of the 18 males tested. In contrast, and regardless of their light treatment, most males (13 of 18) showed day-to-

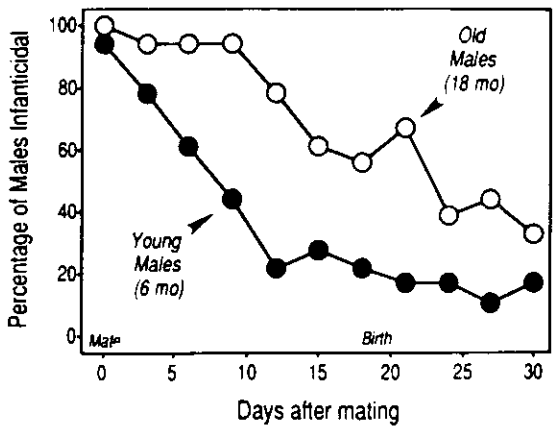

FIG. 5. Males kept in a light:dark 12:12 environment remained individually housed until 18 months of age, at which time the 18 survivors (of 28) were again mated and retested for infanticide every 3 days until 30 days after mating. With regard to individual variation, there was no longer any correlation (as suggested by Fig. 4) between the time elapsed between mating and parenting when a male was 6 months versus 18 months of age ($r^2 = 0.07$, $p > 0.35$). In general, the neural timing mechanism attenuates with age.

day fluctuations in their behavior toward pups before locking in to consistent parenting. These results suggest that the transition phase from infanticide to parenting is a time of considerable behavioral variation and instability, with most males exhibiting oscillations in their reaction to pups (11). In fact, some of the behavioral flip-flops in Fig. 4 look suspiciously periodic.

With regard to individual consistency, the white marker dots shown with each male in Fig. 4 indicate the test day after their first mating 3 months earlier, when each individual expressed parental behavior. Because these males were retested at different intervals (every 3 days vs. every 12 h), no legitimate statistical comparison is possible here. Nevertheless, the visual results agree remarkably well, timewise, from one individual to another. This suggests that after a behavioral cycle is reset, ejaculation will retrigger a new cycle of infanticide inhibition—one that appears programmed to last about the same length of time within a young individual (11). In older males (>18 months of age), however, this temporal repeatability disappears. As shown in Fig. 5, the time interval between mating and the expression of parental behavior was significantly delayed and attenuated in older males when compared with their response when young (6 months of age).

OVERVIEW AND GENERAL DISCUSSION

A Proposed Neuroethological Model

Our past and present research has suggested the following physiological model (11,24). As illustrated by Fig. 6, the intense sympathetic stimulus of coital ejaculation greatly amplifies a male's motivation to kill pups: infanticidal phenotypes remain infanticidal whereas virtually all parental phenotypes become infanticidal immediately after mating. It is not surprising that ejaculation triggers such an immediate pup-killing reaction. Female house mice exhibit a strong postpartum estrus within 24 h after parturition; thus, if a virgin male copulates with a newly lactating female, he will maximize his reproductive advantages by immediately seeking out and destroying her litter.

Ejaculation also activates the time-delayed inhibition process. The neural sub-

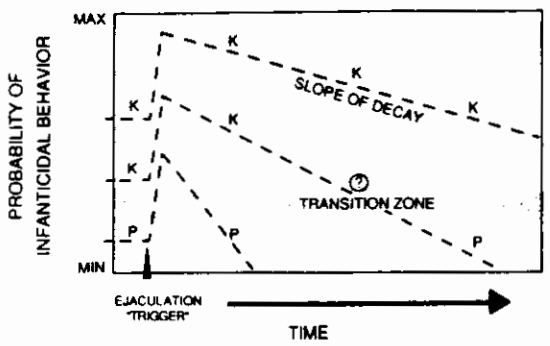

FIG. 6. A mechanistic scheme for examining individual timing variation in the post-ejaculatory inhibition of infanticide (see text). Males who behave parentally (P) before they mate are thus triggered by the act of ejaculation to exhibit infanticide, whereas in males who are already infanticidal (K) before they mate, the stimulus of ejaculation simply intensifies their motivation to kill pups. During the inhibition process, variation in the shape and duration of the transition from infanticide to parenting depends on how an individual's decay slope is angled through the transition zone, a threshold where oscillations in behavior are likely to occur (see Fig. 4).

strate(s) governing infanticide appear to undergo an inhibitory decay, which, over the course of time, eventually diminishes a male's motivation to kill pups. Once an individual's threshold for the inhibition of infanticide is reached (transition zone in Fig. 6), then parental behavior can emerge. Specifically, the inhibition of infanticide seems to unmask the expression of parental behavior. Also implicit in the Fig. 6 scheme is that when a male is exposed to a pup at or near his behavioral threshold (i.e., the transition zone) during the inhibition process, then any one of three behavioral states can occur: infanticide (K), parenting (P), or ignoring the pup. Ignoring is a neutral behavior in which males neither harm nor retrieve pups to their nest (12,24). Although this last behavior occurs infrequently, CF-1 males tend to ignore pups mainly during the unstable transition phase between infanticide and parenting (11).

Finally, variation in the slope (time course) and threshold of a CF-1 male's behavioral inhibition appear programmed to a large extent by hormonal events related to his fetal position, although light cues, genetic differences, and social factors (e.g., synergistic female cues) all seem to interact in shaping this decay process. In fact, there are always a few CF-1 mice (~10–15%) that simply do not respond to the stimulus of ejaculation; some males always remain parental and some always kill pups and, as described earlier, these behavioral phenotypes are correlated with intrauterine position. Among those few individuals in which mating per se does not seem to inhibit pup-killing, the stimulus of ejaculation and female cohabitation are probably both required in order to inhibit infanticide (7,9,26). With regard to aging, the time interval between mating and parenting was consistent in individual young males (6–9 months of age, Fig. 4), but in older males (18 months of age) this time interval was significantly longer (Fig. 5); in fact, 28% of the older males never ceased killing pups. This suggests that the aging causes a shift in response thresholds and changes the male's sensitivity to redundant female cues (9,11).

Male versus Female: Different Systems for Time Measurement

Infanticide is also a fundamental component of the reproductive strategy of female house mice; pregnant females routinely kill pups up to the time of parturition (8,18). Thus, both sexes exhibit infanticide and share a common suite of parental behaviors

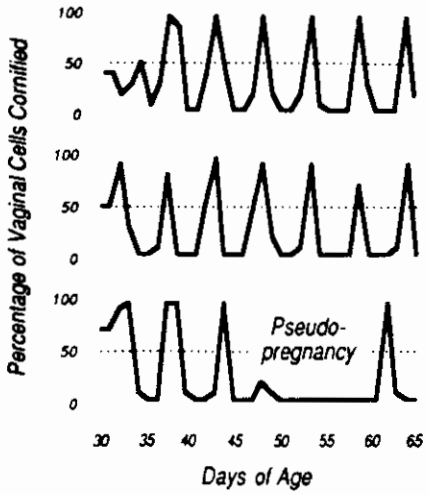

FIG. 7. The development and organization of regular 4- to 5-day estrous cycles in young female house mice maintained at light:dark 12:12. Vaginal smears (using an eyedropper filled with saline) were performed at lights on each day and examined under a microscope. Each peak in cornified epithelial cells indicates ovulation and behavioral estrus. In one of the young females, mechanical stimulation of her vagina with the eyedropper (mimicking copulation) accidentally induced pseudopregnancy, resulting in a temporary cessation of estrous cycles for 2 weeks.

expressed during the time of lactation. During pregnancy, however, female rodents rely on cues from developing fetuses and always seem to gauge the length of gestation in relation to absolute time (27,28), even when entrained to extreme T-cycles mimicking a 20-h versus 28-h day (29, unpublished observations).

As a general rule, however, most reproductive phenomena in females are photoperiodically mediated, such as the preovulatory surge in pituitary luteinizing hormone (LH) and, hence, the organization of regular estrous cycles, which routinely occur at exact 4- to 5-day multiples of the daily light/dark cycle (30,31). Furthermore, there is an interesting neural parallel for time measurement also triggered by copulation in the female mouse. Mechanical stimulation of her vagina by an intromitting penis (or an artificial probe) activates a twice-daily surge of prolactin lasting for 10–14 days after a female mates (32,33). If implantation does not take place, these rhythmic, phase-locked prolactin surges cause a temporary, 10- to 15-day cessation of estrous cycles, a condition known as pseudopregnancy (Fig. 7). Although the above events in a female mouse are all mediated by cyclic changes in the secretion of pituitary and gonadal hormones, neither castration nor ablation of the pituitary gland (which eliminates LH and prolactin) will prevent the time-delayed inhibition of infanticide in mated CF-1 males (24). This suggests that male mice have evolved a novel physiological timekeeping solution for synchronizing their behavior toward pups with the reproductive cycle of their mates (17).

CONCLUSIONS

Finally, we have made no attempt to explain how infanticidal behavior spontaneously reemerges in male mice 2 months after mating. In general, the presence of light seemed to inhibit infanticide during this phase, too (11). No simple physiological explanation can account for these time-delayed responses, and little more can be said here except that our recent experiments suggest both parallels and paradoxes with widely studied behavioral and reproductive timing processes (34,35). Ablation of the

suprachiasmatic nucleus, exposure to high-intensity constant light (both of which disrupt circadian rhythms), or maintenance at skeleton photoperiods are several potential experiments that could distinguish whether light has a photoperiodic, direct, or some other peculiar regulatory role in the timing of this entire behavioral cycle.

There is a final caveat here, too. House mice are known for their enormous reproductive, behavioral, and photoperiodic flexibility (26,36,37). They breed vigorously in a wide variety of feral situations, including circumstances where photoperiodic cues may be irregular or even nonexistent (e.g., building interiors and caves). Likewise, the study of infanticide among various wild and laboratory house mouse stocks has shown a variety of independent and/or multiple cueing mechanisms evolved to inhibit infanticide in male mice: ejaculation, female cohabitation, and social subordination (8,9,14,15,38,39). The proper timing of infanticidal and parental behavior is at the core of a male's reproductive success; thus, from an ecological standpoint, one should not be surprised by the evolution of redundant, backup inhibitory systems operating in the absence of typical temporal or social cues. Given the house mouse's behavioral flexibility, neither can we be certain whether the same or independent inhibitory mechanisms were responding to the various experimental treatments imposed here. However, Elwood (40) noted that in some male house mice, one day of female cohabitation elevates male parental behavior 2 weeks later, suggesting that ejaculation and cohabitation may operate via the same timing mechanism. But regardless of how these behavioral shifts are neurally timed, the prolonged time interval between ejaculation and the inhibition of infanticide (and onset of parental behavior) seems to redefine the range of potential time-dependent relationships between a stimulus and its response.

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