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Female behaviour plays a critical role in controlling murine pregnancy block

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Exposure of recently mated female rodents to unfamiliar male scents during daily prolactin surges results in pregnancy failure (the ‘Bruce effect’). Control of nasal contact with male scents during these narrow windows of sensitivity could allow females to maintain or terminate pregnancy, but female behavioural changes specifically during this critical period have not been investigated. We examined the approach or avoidance of familiar stud strain and unfamiliar male scents by recently mated female mice. Females that maintained pregnancy avoided both unfamiliar and familiar male scent during critical periods of susceptibility for the Bruce effect. By contrast, females that did not maintain pregnancy showed a sharp rise in the time spent with unfamiliar male scent during this critical period. Manipulation of the social status of unfamiliar and stud strain scent donors did not affect the likelihood of pregnancy block, although females spent more time with dominant male scents across all time periods. The ability to control the Bruce effect through behaviour during brief sensitivity just before dusk, when females are likely to be in nest sites, provides a mechanism by which females may adjust their reproductive investment according to nest site social stability and likelihood of offspring survival.

Keywords: behaviour; Bruce effect; mouse; pregnancy block; reproduction; rodent

1. INTRODUCTION

Exposure of female laboratory mice to the urinary scent of an unfamiliar male within a limited time after mating causes pregnancy disruption and return to oestrus (the ‘Bruce effect’, Bruce 1959; Parkes & Bruce 1961). Since its discovery in mice, pregnancy block has been confirmed in several other murine and microtine rodent species (e.g. Storey 1986; de la Maza *et al.* 1999; Mahady & Wolff 2002). Pregnancy disruption is triggered by semiochemicals in rodent urine that are pumped into the lumen of the vomeronasal organ following nasal contact with male scent (Meredith & O’Connell 1979; Luo *et al.* 2003). This activates a specific vomeronasal neuroendocrine pathway that inhibits prolactin release (Bellringer *et al.* 1980; Rajendren & Dominic 1993). As prolactin is essential for maintaining luteal function during early pregnancy in rodents (Stormshak *et al.* 1987), this inhibitory pathway causes luteolysis and hence pregnancy failure. The duration of sensitivity to pregnancy-blocking signals varies between species, ranging from 4 to 5 days post-mating (pre-implantation) in *Mus* (Parkes & Bruce 1961) up to 17 days post-mating (pre- and post-implantation) in microtine species (Stehn & Jannett 1981).

The timing of exposure to unfamiliar male scent is critical. Around oestrus, female rodents show daily prolactin surges, increasing to twice daily after mating and peaking approximately 1 hour before the change to light and dark periods (Barkley *et al.* 1978; Ryan & Schwartz 1980). Pregnancy block occurs only if females are exposed to male scent coincident with two prolactin peaks, at least one during the light phase, while exposure outside these peaks fails to cause pregnancy block (Rosser *et al.* 1989).

During the 4–6 hours period after mating, females learn the scent signature of the stud male, with memory formation contingent on mating (Kaba *et al.* 1989; Brennan *et al.* 1990). Exposure to the stud male’s scent after mating, or to scent from males that are genetically identical to the stud male, fails to disrupt pregnancy (Bruce 1960; Rüllicke *et al.* 2006) and may reduce the likelihood of pregnancy block if females are concurrently exposed to unfamiliar male scent (Kumar & Dominic 1993). Studies commonly define familiar and unfamiliar males according to whether they are from the same or different inbred strain of genetically identical individuals, such as C57BL/6, CBA or BALB/c (e.g. Yamazaki *et al.* 1983; Rosser *et al.* 1989; Peele *et al.* 2003). In addition, others have suggested that socially dominant males may be more likely to trigger pregnancy block, as females that terminate gestation and remate with such animals could reduce the risk to their offspring from infanticidal behaviour by non-stud males (Labov 1981a; Huck 1982).

Despite extensive research into the neurophysiological mechanisms and scent stimuli that cause pregnancy block, the functional significance and evolutionary advantage of this response to females under natural conditions remains an enigma (Bronson & Coquelin 1980; Brennan & Peele 2003). A substantial barrier to understanding the natural circumstances of this response is that the laboratory studies generally prevent females from controlling their exposure to male cues, either through the use of small cages or by applying stimuli directly to the female nares. However, females may be able to control their exposure to scents that elicit pregnancy block under more free-ranging conditions, given the very narrow window of sensitivity around dawn and dusk over a few days after mating (when females are likely to be within their nest sites), and the requirement for females to actively contact and pump

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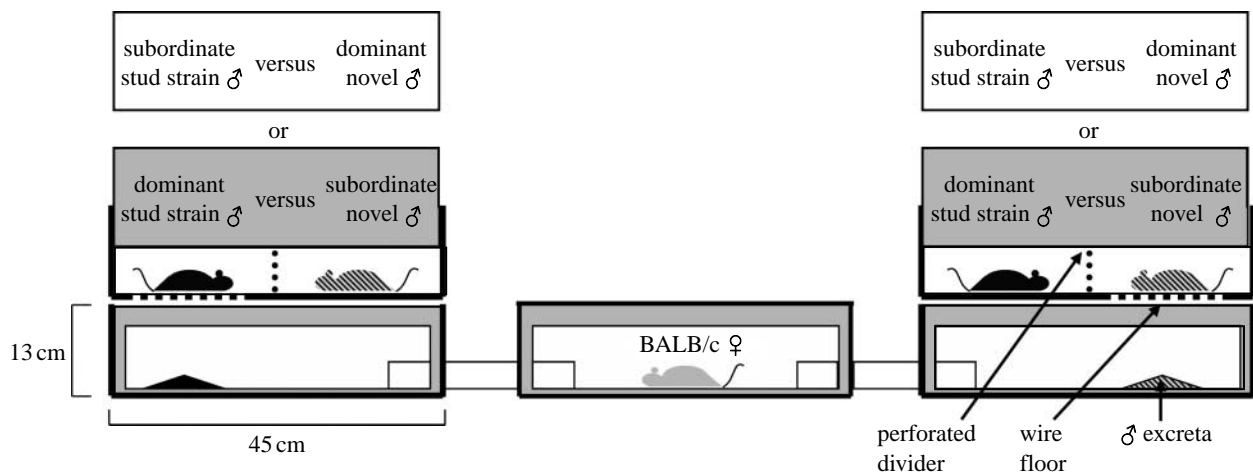


Figure 1. Divided female home area. Male pairs comprising one dominant and one subordinate animal of different strains separated by a perforated perspex screen were housed directly above cages accessible to the female via tunnels linking them to a central 'refuge' cage. One male of each pair was housed on a wire floor to allow excreta to fall into the female's area below. Male pairs were arranged such that females could investigate excreta from a subordinate stud strain male versus dominant novel male (white box) or dominant stud strain male versus subordinate novel male (grey box).

scents to the vomeronasal organ. This could provide females with a mechanism to terminate investment in gestation and subsequent lactation under particular circumstances, where survival of their offspring is at risk because the nest sites cannot be effectively defended against disturbance from unfamiliar animals (Becker & Hurst 2008).

Earlier studies on the behaviour of recently mated females towards male scents are conflicting. Drickamer (1989) found a general avoidance of unfamiliar male scent during the early stages of gestation when wild-derived females were presented with paired samples of soiled male bedding. Conversely, deCatanzaro & Murji (2004) reported attraction of inbred CF1 females to unfamiliar male scent. However, neither of these studies tested females during the sensitive period for the Bruce effect.

Here, we investigate whether recently mated females control their exposure to male scent cues at critical times for pregnancy block, in relation to whether or not they maintain pregnancy. The implications of female control of scent exposure for the functional significance of the Bruce effect under natural conditions are discussed.

2. MATERIAL AND METHODS

(a) Animals

Subjects were 23 adult (10–14 weeks old) BALB/c female mice (obtained at seven weeks of age from Harlan UK Ltd., Oxon, UK), housed in MB1 cages (45 × 28 × 13 cm, NKP Cages, Rochester, UK) on corn cob absorb 10/14 substrate with shredded paper nest material, with food and water provided ad libitum. BALB/c, rather than wild females, were used for this study as they are known to undergo reliable and robust pregnancy block in response to male scent (e.g. Leinders-Zufall *et al.* 2004), unlike in wild-stock mice where pregnancy may also be terminated owing to apparently minor stressors, such as handling or cage cleaning (Chipman & Fox 1966). Scent stimuli were provided by six male pairs (age and source as female subjects), each comprising one C57BL/6 and one CBA/Ca animal housed in MB1 cages, separated from one another by a central perforated perspex divider that allowed continuous olfactory and visual contact, but prevented direct interaction. Twelve C57BL/6 stud males

were housed individually in M3 cages (48 × 15 × 13 cm). Rooms were maintained at 20 ± 1°C, ventilated at 20 air changes per hour, and under a 10/14 hours reversed dark-light cycle (lights off at 10.00–20.00 hours). Behaviour during the dark phase was recorded under dim red light. After completion of this project, animals were kept for use in breeding programmes and further behavioural studies.

(b) Experimental procedure

The experiment was designed to monitor the location of recently mated females with respect to three separate sectors of their home area, during times known to be critical for the Bruce effect. Each of the two outer sectors contained scent from a male of either the same or a different strain to the familiar stud male, while the males also differed in dominance status. The central sector contained no male scent, and cross-contamination between sectors was minimized by the use of relatively narrow communicating access tunnels. By providing an area free from male scent, this design allowed females to control their exposure under circumstances likely to mimic free-ranging conditions.

BALB/c females were singly housed from the start of the experiment, and exposed to mixed cage substrate from males of both the C57BL/6 and CBA/Ca inbred strains to induce oestrus, which was monitored by daily vaginal cytology (samples collected at 10.00–10.30 hours). Females in oestrus were paired with a C57BL/6 stud male ($n=12$), and after observation of mating the pair was left undisturbed for a further 4–8 hours to allow the female to form an adequate memory of stud male scent (Rosser & Keverne 1985; Keverne & Brennan 1996). Conception rate in BALB/c females is relatively high, and it was anticipated that most matings would lead to pregnancy (Nagasawa *et al.* 1973). Non-mated control females ($n=11$) were also used in oestrus, and were subject to the same delay between oestrus detection and introduction to the divided home area as females that mated.

Each mated and control female was transferred to a set of three linearly adjacent MB1 cages, linked by perspex tunnels (15 cm length × 5 cm diameter), and each fitted with transparent side panels covering approximately 80 per cent of the cage wall to allow visualization of the female (figure 1).

Food, water and bedding were provided in the central cage, which was free from male scent. Males were housed in two MB1 cages suspended approximately 10 mm above opposite end cages of the female residence. Each male cage contained a pair of animals, comprising one male from the same genetically identical inbred strain as the stud male (C57BL/6) and one from a novel strain (CBA/Ca, previously shown to cause pregnancy block; *Peele et al.* 2003). Males were separated from one another by a central perspex divider, with one animal housed on a solid floor and the other on wire flooring (9 mm, 15 g stainless steel; Arrowmigh, Hereford, UK). The wire flooring below one male of each pair allowed fresh excreta of only the required scent donor to fall into the female's cage below, while allowing males to be housed in pairs to maintain dominance relationships (see below).

Female behaviour was video recorded remotely to prevent disturbance, and location was noted every 6 s in 5 min bins for 90 min preceding lights on or off ('dawn' or 'dusk', respectively) over 48 hours. Females were then transferred to a clean MB1 cage, and pregnancy was confirmed by the birth of offspring after 19–20 days.

To provide a functional context in which females might choose either to block or maintain pregnancy according to preference for the novel male as a mate, the dominance status of the two male scent donors was manipulated such that in half the tests the novel CBA/Ca male was dominant, and thus might be preferred by the female, while in the other half the stud strain male was dominant (*Huck 1982*). To produce socially dominant and subordinate mice, pairs of C57BL/6 and CBA/Ca males were housed in MB1 cages, separated from one another by a central perforated perspex divider that allowed continuous olfactory and visual contact but protected the males from physical aggression. Pairs were allowed to interact for 5 min twice daily until a clear hierarchy was established after approximately two weeks (when dominant males initiated all interactions and subordinates always attempted to avoid the dominant). To prevent injury, aggressive encounters were stopped after 5 s fighting or 10 s chasing and the stable hierarchy was maintained by once daily interactions as above. Two CBA/Ca and four C57BL/6 males became clearly dominant, and four CBA/Ca and two C57BL/6 clearly subordinate. Females were then tested with either a dominant C57BL/6 male from one male pair versus a subordinate CBA/Ca male from another male pair or vice versa.

(c) Statistical analysis

Data were combined into four 45 min periods to examine behaviour during (90–45 min) or after (45–0 min) expected prolactin peaks near the end of the dark and light periods. The proportion of time spent in each cage of the choice apparatus was arcsine transformed for analysis by repeated-measures general linear model (GLM) using the SPSS software package (v. 11.0.0).

3. RESULTS

Control unmated females showed no preference between areas containing scent from a CBA/Ca male, a C57BL/6 male or no scent, spending equal time in each of the three cages across all four time periods (during and after known prolactin peaks in the light and dark phase; *figure 2*). By contrast, the location of recently mated females differed according to whether or not they maintained pregnancy as predicted. The four mated females that maintained

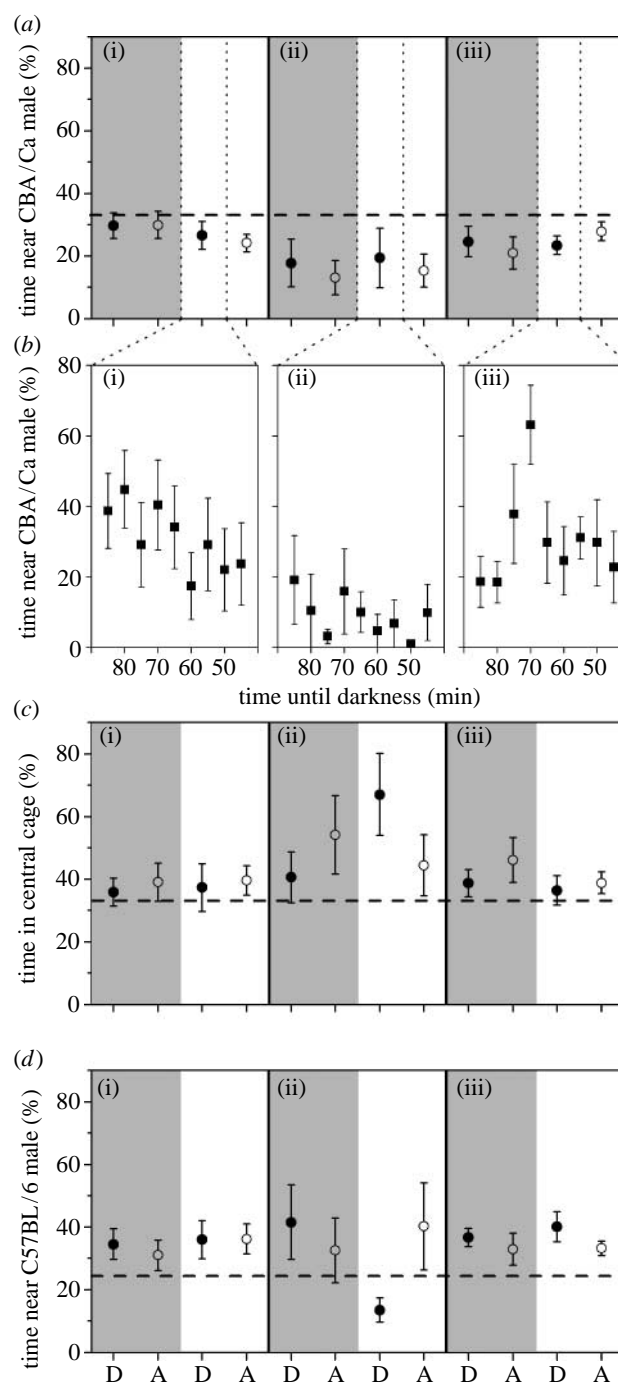


Figure 2. Proportion of test time spent by females in the vicinity of different males during (D, filled symbols) and after (A, open symbols) expected light and dark phase prolactin peaks (90–45 min and 45–0 min prior to lights change, respectively) when females were housed in three interlinked cages over 48 hours (mean % time \pm s.e.) ((i) unmated, (ii) pregnancy maintained and (iii) pregnancy blocked). Dashed line represents random distribution across cages. (a) Time in the cage containing novel CBA/Ca strain male scents across all time periods (effect of pregnancy maintenance: $F_{1,10} = 5.99$, $p = 0.034$). (b) Time near novel CBA/Ca male during the most sensitive period (90–45 min before dark) divided into 5 min bins. (c) Time in central cage with no male scents (interaction between pregnancy maintenance, light phase and time period: $F_{1,10} = 5.60$, $p = 0.04$). (d) Time in cage containing familiar C57BL/6 (B6) stud strain scents (interaction between pregnancy maintenance, light phase and time period: $F_{1,10} = 6.46$, $p = 0.029$). Unmated controls showed no preferences between the three cages.

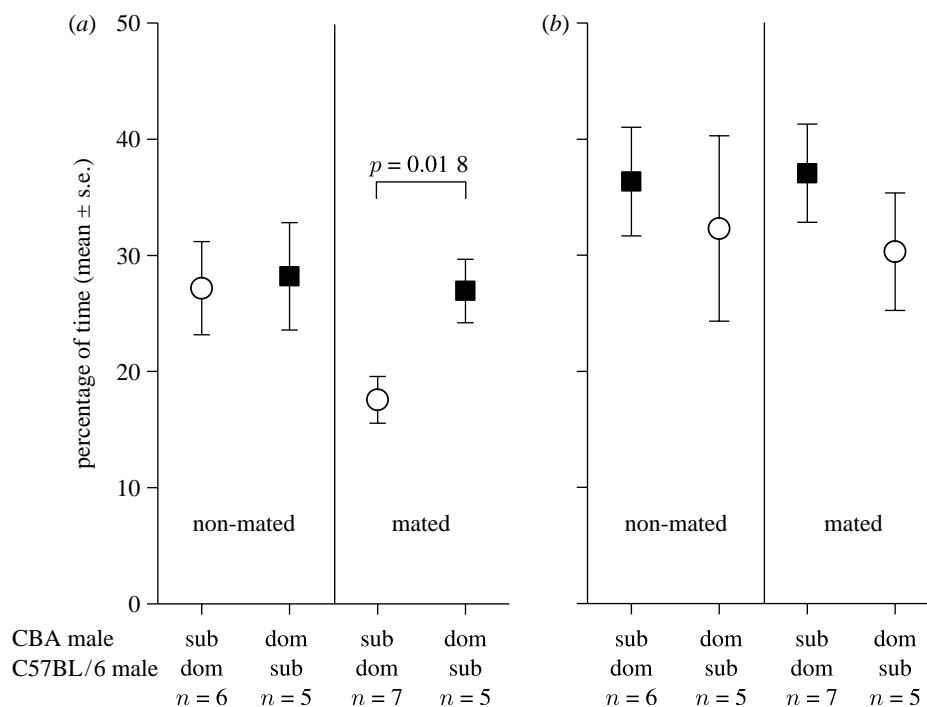


Figure 3. Percentage of the total time spent by all females in the vicinity of subordinate (sub; circles) and dominant (dom; squares) males of (a) unfamiliar (CBA) and (b) familiar (C57BL/6) strains.

pregnancy (33%) spent significantly less time near novel CBA/Ca male scent than the eight females that blocked pregnancy (67%), a bias that was consistent over all four time periods ($F_{1,10}=5.99$, $p=0.034$; figure 2a). This difference reflected a general avoidance of novel male scent by the newly inseminated females that maintained pregnancy compared with unmated controls ($F_{1,13}=6.76$, $p=0.022$). By contrast, those that did not maintain pregnancy spent similar time overall near to novel CBA/Ca male scent compared with unmated control females ($F_{1,17}=0.80$, $p=0.39$). However, during the critical light period corresponding to the expected peak in prolactin when mice are sensitive to the Bruce effect, females that failed to maintain pregnancy showed an unusual sharp rise in time spent with novel male scents 70–75 min before dark that coincided across individuals and days (figure 2b). Similar peaks in coincident attraction to novel male scent were not seen during any other time period or by other females. This may reflect a specific attraction to novel male scent on reaching a threshold level of prolactin among females that did not maintain pregnancy, but the precise timing of these hormonal changes is unknown. Over this same sensitive light period, 90–45 min before dark, females that maintained pregnancy spent very little time with novel male scent, significantly less than those that blocked ($F_{1,10}=5.97$, $p=0.035$; figure 2b).

Females that blocked pregnancy in response to novel male scent consistently spent one-third of their time near familiar stud strain scents, similar to unmated controls (figure 2d). However, those that maintained pregnancy avoided not only novel male scent, but also the scents of stud strain males specifically during the critical time period corresponding to the light phase prolactin peak (interaction between pregnancy maintenance, light phase and time period: $F_{1,10}=6.46$, $p=0.029$; figure 2d). At first sight, this avoidance of scent from the familiar stud strain seems surprising, as this scent does not induce

pregnancy block (Bruce 1960; Keverne & de la Riva 1982). However, this was matched by a simultaneous increase in time spent in the central cage away from both male scents (interaction between pregnancy maintenance, light phase and time period: $F_{1,10}=5.60$, $p=0.04$; figure 2c). Thus, females maintaining pregnancy avoided approaching the scents of either male during a short critical time period between 90 and 45 min before dark on the first 2 days following insemination, regardless of the efficacy of the scents to block pregnancy, while those that failed to maintain their pregnancy did not ($F_{1,10}=7.43$, $p=0.021$).

There was no evidence that male social status influenced the Bruce effect. Mated females spent more time near a novel male when it was dominant across all time periods ($F_{1,10}=7.94$, $p=0.018$; figure 3), confirming the well-established preference of female mice for dominant males (Hurst 1987). However, they did this whether they maintained or blocked pregnancy, and there was no indication of any difference in this preference during the sensitive period for pregnancy block.

4. DISCUSSION

This experiment demonstrates that female mice are able to control whether or not gestation is blocked by choosing to, respectively, contact unfamiliar male scent or avoid all male scent at sensitive times for the Bruce effect. How many non-pregnant females underwent pregnancy block, and how many developed pseudopregnancy from an infertile mating was unknown. However, as conception rate in BALB/c mice is high (Nagasawa *et al.* 1973), very few pseudopregnant animals were expected.

As previously discussed, pregnancy block occurs only if females are exposed to male scent coincident with two prolactin peaks, at least one during the light phase, while exposure outside these peaks fails to block pregnancy (Rosser *et al.* 1989). It was suggested above that the unusual sharp rise in time spent with novel male scents by

blocking females, observed 70–75 min before dark, may reflect a specific attraction to novel male scent on reaching a threshold level of prolactin among these females. Rodent prolactin levels have been shown to influence several behaviours that may affect reproductive success, including mating strategy (Schradin 2008), parental behaviour (Storey *et al.* 2006) and anxiety (Torner *et al.* 2001). Changes in prolactin through the oestrus cycle have been measured in trunk blood in a limited number of serial sampling studies in mice (Michael 1976; Barkley *et al.* 1978; Ryan & Schwartz 1980). While these studies confirm that a surge in prolactin occurs approximately 1 hour before dark, in all cases measurements were taken at intervals of 1–2 hours. Thus, it remains unclear about how the observed behaviour of females in the present study might correspond to specific changes in prolactin secretion at a finer temporal scale.

Female control of exposure to male scent at critical times may help to explain why similar pregnancy-blocking stimuli have produced conflicting results in earlier experiments. Many early studies into the Bruce effect appear to assume that it evolved for male advantage (reviewed by Schwagmeyer 1979), and the presence of a male or his scent are assumed to result inevitably in female exposure (e.g. Bruce 1963; Labov 1981*a*; Huck 1982). Correspondingly, most experimental designs have attempted to prevent females from controlling exposure to male scent, but this may not have been achieved in some cases. For example, in one study examining how the social status of males influenced their ability to trigger pregnancy block (Labov 1981*a*), females were housed directly below males, while a similar study (Huck 1982) housed females adjacent to males, separated by mesh. The pregnancy-blocking ability of dominant males was equal to subordinate males in the former study, but more efficacious in the latter. As the former study enforced female proximity to male scent while the latter did not, it is possible that females were able to exert some control over their exposure to male scent in the apparatus used by Huck (1982) but not by Labov (1981*a*). In addition, in the design described by Huck, the social status of the male scent donor may have influenced the intensity of contamination of the female area with male scent. As dominant males produce copious scent marks throughout their territory, while subordinates do not (Desjardins *et al.* 1973), contamination of the female area with male scent is likely to have been greater when adjacent to a dominant, rather than a subordinate male. In the present study, male social status had no effect on the likelihood of pregnancy block, supporting the findings of Labov (1981*a*).

Central to many of the arguments for male reproductive advantage in pregnancy block is the assumption that females will remate with the blocking male after terminating their current gestation, but this behaviour has not been demonstrated except in situations of enforced cohabitation (Labov 1981*b*). Indeed, females able to evade such male-induced reproductive costs are likely to be at a significant evolutionary advantage, and intriguingly, in tests conducted under free-ranging conditions, females maintained pregnancy despite artificial replacement of stud males in their enclosure (Mahady & Wolff 2002).

The adaptive advantages of a passive female response to male scent have been queried repeatedly (e.g. Bronson & Coquelin 1980; Brennan & Peele 2003), and several authors

have proposed hypothetical female advantages for the Bruce effect. These include enabling the female to remate if deserted by the original stud male (Dawkins 1976), avoidance of male infanticide (Labov 1981*b*; Storey 1986) or post-copulatory mate choice for a preferred stud male (Labov 1981*a*; Huck 1982; Coopersmith & Lenington 1998; Rüllicke *et al.* 2006).

The issue of timing has frequently been overlooked in previous studies, but appears to be of critical importance in the interaction between behaviour and pregnancy block. By altering their exposure to male scent during brief periods of sensitivity, females could choose to maintain or terminate pregnancy in the presence of unfamiliar male scent with minimal impact on normal behaviour at other times. Recently, we proposed that females could use pregnancy block to terminate investment in gestation where risk to offspring survival was increased (Becker & Hurst 2008). Females that maintained pregnancy in the present study avoided the scents of all males during the critical sensitive period for the Bruce effect, regardless of the efficacy of the scents to block pregnancy, by remaining mostly in the central cage. Females that do not explore areas containing male scents during the critical period may avoid accidental exposure to close nasal contact with the scents of unfamiliar males, particularly given the propensity of males to countermark each other, which increases the risk that familiar and unfamiliar scents may be found together.

Furthermore, the sensitive period, occurring approximately 1 hour before dark (Rosser *et al.* 1989), coincides with the time females are most likely to be in sheltered nest sites (Refinetti 2004). If females remain within the nest during this sensitive period, their exposure will be restricted to other animals that share their nest through the light phase. Social disruption of maternal behaviour has been suggested as the main factor affecting offspring survival in mice (Peripato *et al.* 2002). Its importance can be seen in the sharp decrease in pup survival, and hence female reproductive success, in nest sites that cannot be defended effectively, particularly those used by a large number of animals including non-stud males (Southwick 1955). Pregnant females strongly defend their nest sites (Vom Saal *et al.* 1995), but their ability to do so depends on the physical protection afforded by the site and social pressure to use limited sites of shelter (Wolff 1985; Hurst 1987). The presence of fresh scents from other males, particularly from outside a familiar stable group, would indicate a nest site not defended effectively. Avoidance of male scents would allow pregnant females to avoid settling in such sites and, since pregnancy block occurs only in response to fresh scent (Peele *et al.* 2003), by the end of the light phase females will have had ample opportunity to exclude males or to leave the nest for an alternative. However, where this is not possible (e.g. because defensible nest sites are limited), females that terminate pregnancy until they can find a more suitable nest will avoid wasted investment, particularly prior to implantation.

Thus, rather than providing a reproductive benefit to males as traditionally assumed, the Bruce effect may have evolved solely to female advantage. Investigation of how the apparent stability of nest sites influences the outcome for the maintenance or blocking of pregnancy, and the analysis of remating strategies following pregnancy block, including paternity and the subsequent willingness of

females to remate, will be essential to evaluate the advantages and disadvantages of the Bruce effect from both a female and male perspective.

All experimental work was undertaken according to the ASAB/ABS guidelines for the treatment of animals in behavioural research and teaching (ASAB/ABS 2006).

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