Effects of Intrauterine Position on the Behavior and Genital Morphology of Litter-Bearing Rodents

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We review the literature describing hormonally mediated effects of intrauterine position on the genital morphology and reproductive behaviors of litter-bearing rodents. We emphasize work carried out in our own laboratory in which male and female Mongolian gerbils served as subjects. The results of the studies we consider indicate that biologically significant aspects of the variance in morphology and reproductive strategy seen in all populations of adult rodents reflect variance in perinatal levels of exposure to gonadal hormones induced by intrauterine position. We conclude that studies of correlations between intrauterine position and adult characteristics provide opportunities to examine the impact of normal variation in perinatal exposure to hormones on adult mammalian phenotypes.

Variation in perinatal exposure to gonadal hormones produces variation in the characteristics of adult mammals (Becker, Breedlove, & Crews, 1992). Consequently, identifying features of the perinatal environment that alter exposure to gonadal hormones received by animals early in life can help to explain the phenotypic variability found in natural mammalian populations. Such explanation is potentially important because whenever we can identify a cause of apparently random variations in phenotype, we increase not only our basic understanding of the biological world, but also our ability to control events that may affect the lives of both humans and other animals.

Laboratory studies of domesticated rodents have identified several charac-

teristics of the normal uterine environment that can cause fetal mammals to receive differing levels of exposure to gonadal hormones. We focus here on effects of one of these features of intrauterine life, intrauterine position (IUP), on both perinatal exposure to hormones and the adult phenotypes of male and female rodents.

IUP EFFECTS ON THE GENITAL MORPHOLOGY AND BEHAVIOR OF RODENTS

House Mouse and Norway Rat

In many litter-bearing rodent species such as the house mouse (*Mus domesticus*) or Norway rat (*Rattus norvegicus*), the IUP that a male or female fetus occupies relative to fetuses of the same or opposite sex influences the hormonal milieu in which that fetus matures (Clemens, Gladue, & Coniglio, 1978; Gandelman, vom Saal, & Reinisch, 1977; Meisel & Ward, 1981). For example, male mouse fetuses that occupy IUPs between two male fetuses (2M males) have greater blood concentrations of testosterone (T) than do brothers maturing in IUPs between two female fetuses (2F males).[1] Similarly, female fetuses located between males (2M females) have higher T titers than do their sisters gestated between females (2F females).

The opposite relation is observed for blood concentrations of estradiol (E); mouse fetuses of both sexes from 2F IUPs have significantly greater blood concentrations of E than do fetuses of the same sex from 2M IUPs (vom Saal, Grant, McMullen, & Laves, 1983), and levels of both T and E found in fetal rodents that develop in IUPs between one male and one female fetus are intermediate between those of fetuses that develop in 2M and 2F IUPs (vom Saal, 1984, 1989).

Although there has been some controversy as to how steroid hormones travel from one fetus to the next and, consequently, as to whether the sex of immediate intrauterine neighbors is the most important determinant of levels of fetal exposure to T (Houtsmuller, Juranek, Gebauer, Slob, & Rowland, 1994; Houtsmuller & Slob, 1990; Meisel & Ward, 1981; Richmond & Sachs, 1984), recent studies both of dye transport within the uterus of pregnant mice and of movement of radioactively labeled T between fetuses indicate that androgens secreted by the gonads of male fetuses late in gestation diffuse through the amniotic fluid and cross fetal membranes to adjacent fetuses (Even, Dhar, & vom Saal, 1992; vom Saal & Dhar, 1992). This diffusion causes fetuses located between male fetuses to receive relatively high levels of exposure to exogenous T during prenatal development.

Genital morphology. In house mice, several hormonally sensitive, morphological features have been reported to be correlated with IUP, including anogenital distance (AGD), body weight (Kinsley, Miele, et al., 1986), seminal vesicle weight, and prostate gland and preputial gland weights (Even & vom Saal, 1991; Nonneman, Ganjam, Welshons, & vom Saal, 1992). AGD has received the greatest attention.

At birth, the amount of tissue that separates the anus and genital papilla of 2M females is greater than the corresponding amount of tissue in 2F females (Clemens et al., 1978; vom Saal & Bronson, 1978, 1980). By using a weight-corrected index of the AGD in female house mice, it may also be possible for researchers to discriminate female mice from 2M and 2F IUPs as adolescents (Vandenbergh & Huggett, 1995).

As would be expected if observed differences in AGD at birth found in female rodents are mediated by their prenatal levels of exposure to T, administration of antiandrogens to either pregnant rats (Clemens et al., 1978) or pregnant mice (vom Saal, 1989) increases the AGD of their female offspring.

Behavior. Effects of IUP on the reproductive behavior of mice are numerous. Male mice from 2M IUPs are more aggressive and (perhaps unexpectedly) less sexually active, less infanticidal, and more paternal than are their male littermates from 2F IUPs (vom Saal, 1984, 1989).

Female mice from 2M IUPs have their first estrus at a later age than do their sisters from 2F IUPs. The former animals have longer estrus cycles and a shorter reproductive life than do the latter. They give birth to fewer litters during their lifetimes and to a greater percentage of males per litter. They are also both less attractive to males and more aggressive toward other females than are females from 2F IUPs (Kinsley, Konen, Miele, Ghiraldi, & Svare, 1986; Vandenbergh & Huggett, 1995; vom Saal, 1984, 1989; vom Saal & Bronson, 1978).

Some investigators have failed to observe some effects of IUP on behavior or morphology of female house mice (Jubilan & Nyby, 1992; Simon & Cologer-Clifford, 1991). However, the reality of IUP effects on the phenotypes of female house mice are suggested by two observations: First, many of these effects have been reported repeatedly both within and across laboratories. Second, parallel and very robust effects of IUP on morphology and reproductive behavior have been found in females of another litter-bearing rodent species, the Mongolian gerbil (*Meriones unguiculatus*).

Mongolian Gerbils

Females. Our interest in the impact of IUP on adult reproduction was the result of a serendipitous discovery made while routinely recording the age at vaginal

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[1] At different times during the exploration of IUP effects, different classification schemes have been used to assign fetuses to IUPs. To simplify the exposition, we discuss all experiments as though fetuses had been classified in terms of the number of both adjacent male and adjacent female fetuses, although that was not always the case in the original research.

opening of female Mongolian gerbils as one of a number of measures of their rate of maturation (Clark & Galef, 1985). We found that age at vaginal introitus was bimodally distributed in our colony; some females exhibited vaginal perforation before their eyes opened on Day 16 postpartum, others only after they were weaned on Day 25, and there was a period from Day 22 to 27 when essentially no vaginal opening occurred (Clark, Spencer, & Galef, 1986).

When we examined the entire reproductive lives of samples of these early- and late-maturing gerbils, we found marked differences in their reproductive profiles. Early-maturing females (a) were less likely to behave aggressively toward others; (b) were more likely to be impregnated by strange males with whom they were paired than were late-maturing females (Clark et al., 1986); (c) reproduced for the first time at an earlier age; (d) had more litters during their lifetimes; (e) produced more young in each litter and, consequently, over a lifetime; and (f) produced more than twice as many offspring as did late-maturing females.

Further, at both delivery and weaning, litters of early-maturing females contained a greater proportion of daughters than did litters of late-maturing females, and a greater proportion of the females in the litters of early-maturing than of late-maturing females were themselves early-maturing.

Early-maturing females spent less time and effort caring for their offspring than did late-maturing females: Late-maturing females spent more time nursing their young and were more likely to retrieve pups displaced from the nest than were early-maturing females (Clark & Galef, 1986).

Some differences in the reproductive behavior of early- and late-maturing females reflected reliable differences in their ages at parturition or in the sizes and sex ratios of the litters they delivered. However, even when we controlled experimentally for such factors, differences in the sex ratios of litters produced by early- and late-maturing females persisted, as did differences in the age at sexual maturation of their daughters (Clark & Galef, 1986).

As mentioned previously, early-maturing female gerbils tend to be born as members of relatively large, female-biased litters, whereas late-maturing females are more often members of relatively small, male-biased litters. A necessary consequence of changes in the size or sex composition of litters is change in the probability that any fetus in those litters will occupy an IUP between either two males or two females: As the proportion of males in a litter increases, the probability that a fetus in that litter will occupy a 2M IUP increases; and as the size of a litter decreases, the probability of a fetus being located at the end of a line of pups in a uterine horn increases, so the probability of its being between two fetuses of either sex decreases. Consequently, it seemed reasonable to ask whether, for example, the correlation we had observed between age at sexual maturation of a dam and age at sexual maturation of her daughters was mediated by differences in the IUPs occupied by daughters born to mothers that had matured early or late.

In fact, we found that both the sex ratios of the litters a gerbil dam produced and the rates of maturation of her daughters were affected by her IUP: (a) Females from 2M IUPs delivered litters with a reliably greater proportion of males than did females from 2F IUPs (Clark & Galef, 1994, 1995a, 1995b; Clark, Karpiuk, & Galef, 1993; Vandenbergh & Huggett, 1994, reported a similar effect in house mice); and (b) daughters born to both early- and late-maturing gerbil dams that occupied 2F IUPs were almost sure to be early-maturing themselves, whereas daughters from 2M IUPs born to both early- and late-maturing dams produced roughly equal numbers of early- and late-maturing daughters (Clark & Galef, 1988).

We also found that, within each sex, gerbil fetuses from 2M IUPs had higher circulating levels of T than did gerbil fetuses from 2F IUPs (Clark, Crews, & Galef, 1991), a result suggesting that differences in prenatal exposure to T, consequent on IUP, might mediate the differences we had observed in the reproductive profiles of female gerbils from different IUPs.

However, additional findings indicated that differences in the age at vaginal introitus of daughters born to early- and late-maturing dams could not be totally explained in terms of the IUPs that the dams had occupied: 2M daughters of early-maturing dams that gestated in 2M IUPs were twice as likely to mature early as were similarly located daughters of late-maturing dams, and fetuses located in IUPs between one male and one female fetus and gestated by late-maturing dams had higher blood titers of T than did fetuses in similar IUPs that were gestated by early-maturing dams (Clark et al., 1991).

Thus, although IUP accounted for much variance both in age at vaginal opening and circulating levels of T in female gerbil fetuses, there were clearly additional effects of a dam herself on both levels of gonadal hormones to which her young were exposed and rates of maturation of her daughters. Indeed, we found that, on the last day of gestation, late-maturing dams had higher circulating levels of T and lower circulating levels of E than did early-maturing dams (Clark et al., 1991). Probably, effects of gerbil dams on the reproductive life histories of their daughters, like the effects of IUP on reproductive life histories of female Mongolian gerbils, are mediated by variance in prenatal exposure to gonadal hormones.

Caution in interpreting the correlations between circulating levels of T and E in dams late in gestation and the reproductive profiles of the daughters they bear is appropriate, because it is always possible that the sex ratio of the litter that a dam is gestating is affecting her circulating levels of hormones rather than that a dam's endogenous hormone levels are affecting her fetuses. For example, Clark, Crews, and Galef (1993) examined the frequency of T-dependent behaviors exhibited by individual Mongolian gerbils during successive pregnancies and found that, on the last days of gestation, both the number and proportion of males in the litters females were gestating affected the frequency with which those females scent marked (scent marking in female gerbils is an androgen-sensitive behavior). And, as one might expect, on the last day of gestation, the number and percentage of males in the litters

females were gestating were positively correlated with their circulating levels of T and negatively correlated with their circulating levels of E (Clark, Crews, & Galef, 1993).

Males. IUP has biologically significant effects on the reproductive profiles of male, as well as female, Mongolian gerbils. Indeed, male gerbils gestated in 2F IUPs appear to be at considerable reproductive disadvantage in comparison with their brothers gestated in 2M IUPs.

To compare the potency of male gerbils from different IUPs, we paired individual adult males that had been gestated in 2M and 2F IUPs with a succession of randomly selected virgin females and examined the size of the litter produced by each female with which a male had been paired. We found that males gestated in 2M IUPs sired significantly more offspring than did males gestated in 2F IUPs (Clark, Tucker, & Galef, 1992; Clark, Vonk, & Galef, 1997).

Although litters sired by 2M males were slightly smaller than those sired by 2F males, the primary cause of the reduced fecundity of males from 2F IUPs was their failure to impregnate their consorts. Males from 2F IUPs were five times more likely than were males from 2M IUPs to fail to impregnate a female during a 3-week period of cohabitation with her (Clark, Tucker, & Galef, 1992).

Observation of the reproductive behavior of males from different IUPs revealed apparent inadequacies in the copulatory performance of 2F males that may help to explain at least some of their lack of success in impregnating females. When paired with an unfamiliar virgin female, 2F males exhibited longer latencies to intromit, longer latencies to ejaculate, and were significantly less likely than were 2M males to achieve ejaculation (Clark, Malenfant, Winter, & Galef, 1990; Clark, Vonk, & Galef, 1997). The observed greater sexual success of 2M than of 2F male Mongolian gerbils is not consistent with vom Saal's (1984, 1989) reports of greater sexual activity in 2F than 2M male house mice. However, the apparent inconsistency probably reflects differences in indices of sexual behavior rather than a true interspecies difference in response to IUP. Reported differences in effects of IUP on parental behavior of male house mice and male Mongolian gerbils (discussed later) may also reflect differences in measurement.

Examination of the genital musculature of 2M male gerbils revealed that their bulbocavernosus and levator ani muscles (which wrap around the base of the penis and rectum and mediate penile reflexes involved in copulation; Hart & Melese-d'Hospital, 1983) were roughly 50% larger than were those of 2F males (Forger, Galef, & Clark, 1996). Such deficits in the genital musculature of males from 2F IUPs may have contributed to their relatively limited reproductive success (Sachs, 1982).

In rats, prenatal exposure to T permanently increases the size of the genital musculature by increasing both the number and size of muscle fibers (Breedlove, Jacobson, Gorski, & Arnold, 1982; Cihak, Gutman, & Hanzlikova, 1970; Tobin &

Joubert, 1991), so it is not unreasonable to propose that differences observed in the genital musculature of Mongolian gerbils from different IUPs reflected, at least in part, differences in levels of prenatal exposure to T.

Male gerbils from 2F IUPs suffer from yet another potential reproductive disadvantage. Female gerbils can discriminate 2M from 2F males on the basis of their scents and, when in estrus, prefer to associate with 2M males. Female gerbils not only scent mark more frequently when they encounter the scent marks of 2M males than when they encounter those of 2F males (Clark & Galef, 1994), they also, when in estrus, choose to spend more time near 2M males than 2F males, when given a choice between them (Clark, Tucker, & Galef, 1992).

The differences in the copulatory behavior of adult males from different IUPs and the differing response of females to 2M and 2F males described here may be a result of differences both in the circulating levels of T in adult males from different IUPs and in the responsiveness of males from different IUPs to whatever T is in their plasma. Adult male gerbils that, as fetuses, occupied 2M IUPs, have higher circulating levels of T than do adult male gerbils that, as fetuses, matured in 2F IUPs (Clark, vom Saal, & Galef, 1992). Castrated 2M males are also more responsive to exogenous T than castrated 2F males (Clark, Bishop, vom Saal, & Galef, 1993). Consequently, 2M males should be more likely to express T-sensitive behavioral and morphological characteristics than are their 2F fellows.

The reduced attractiveness to females and lower sexual competence of 2F male gerbils described earlier are also characteristics one might expect natural selection to have acted vigorously to suppress, and there is some evidence that such selection may be at work. By segregating her male and female fetuses in different uterine horns, a gerbil dam could protect her sons from prenatal contact with females and the reduced attractiveness and potency that such contact entails. In fact, female Mongolian gerbils do tend to gestate their male fetuses in their right and their female fetuses in their left uterine horns, thus producing fewer 2F male offspring and 2M female offspring than one would otherwise expect (Clark & Galef, 1990).

The right ovaries of female gerbils produce a greater proportion of male-destined eggs than do their left ovaries. Consequently, when we surgically exchanged right and left ovaries within female gerbils, they produced more male fetuses in their left than in their right uterine horns, whereas females whose left and right ovaries we removed and reimplanted in their original locations, continued to produce more males in their right than in their left uterine horns (Clark, Ham, & Galef, 1994).

There is also evidence of a second way in which gerbil dams may be able to increase the future potency of sons. It has been known for some time that the amount of anogenital licking that a male Norway rat pup receives from its dam before it is weaned can influence the pattern of its copulatory behavior as an adult (Moore,

1983). When adult, those male rats that, as pups, were the recipients of relatively large amounts of anogenital licking by their dams exhibited shorter ejaculatory latencies and shorter interintromission intervals than did brothers that received less anogenital grooming. It is, however, not known whether these variations in copulatory behavior affect the ability to impregnate females (Moore, 1983).

We have found that the greater the number of male intrauterine neighbors a male gerbil pup had while a fetus, the more time its dam spends grooming its anogenital area. In 13 of 16 litters containing pups from more than one IUP, males adjacent to greater numbers of males in utero received a greater amount of anogenital grooming from their dam than did male pups adjacent to fewer males in utero (Clark, Bone, & Galef, 1989). And, as mentioned earlier, there is a correlation between the IUP that a male gerbil fetus occupies and its reproductive success when adult; male gerbils from 2F IUPs that receive relatively little maternal anogenital grooming (like male rats that received little maternal anogenital grooming) have longer ejaculation latencies and longer postejaculatory intervals than do male gerbils from 2M IUPs. Consequently, observed effects of IUP on copulatory performance in male gerbils may be mediated by differences in the amount of anogenital grooming that mothers direct toward pups from different IUPs. Experiments needed to directly test that hypothesis have yet to be conducted.

Whatever the underlying mechanism, the relative lack of reproductive success of 2F male gerbils is difficult to understand from an evolutionary perspective. The fitness costs of reduced potency are obvious; its fitness benefits are more difficult to imagine.

In a thoughtful review of the literature on effects of T on the reproductive behavior of birds, Ketterson and Nolan (1994) described several species in which exposure to high levels of T both increases sexual behavior and decreases parental behavior. They discussed such negative correlations among T-sensitive behavioral traits both as design constraints limiting adaptation and as trade-offs persisting because they permit organisms to adjust their reproductive tactics in response to variations in environmental conditions.

We have recently begun to explore the possibility that adult 2F male gerbils (with low circulating levels of T), although clearly less potent than their 2M brothers (with high circulating levels of T), might exhibit compensatory increases in their parental behavior, increasing their reproductive success by increasing the investment they make in the relatively few young that they do produce. To date, the data are promising. At least in the laboratory, 2F male Mongolian gerbils (unlike 2F male mice; vom Saal, 1984, 1989) are consistently more attentive to young of their species than are 2M males (Clark, Desousa, Vonk, & Galef, 1997). Possibly, under adverse environmental conditions, the relatively great investment that 2F male gerbils are willing to make in their offspring compensates for their reduced potency. Experiments needed to directly test that hypothesis have not been conducted.

Effects of IUP on Sexually Dimorphic Asymmetries in Mongolian Gerbils

Informal observation of young gerbils revealed a phenomenon that we rarely saw in young Norway rats, the other rodent species bred in substantial numbers in our vivarium. Because it was not unusual for one of the eyes of a gerbil pup to open 1 or even 2 days before the other, we frequently found gerbil pups with only one of their eyes open.

We became interested in this asynchronous eye opening because our informal observations suggested that there was a correlation between the sex of a pup and the order in which its eyes opened. A formal study revealed that, indeed, the right eyes of female gerbil pups opened first almost twice as often as did the right eyes of male gerbil pups (Clark, Robertson, & Galef, 1993).

Observation of the order of eye opening in cesarean-delivered male and female gerbils from 2M and 2F IUPs revealed further that, regardless of sex, 2F gerbil pups exhibited primacy of right-eye opening (the female pattern) with significantly higher frequency than did 2M gerbil pups. The influence of IUP on lateralization of eye opening is consistent with the hypothesis that prenatal exposure to gonadal hormones causes the sex-correlated asymmetry in eye-opening we had originally observed (Clark, Robertson, & Galef, 1993), and led us to search for other sexually dimorphic asymmetries in these animals.

In a series of studies, we failed to find, in Mongolian gerbils: (a) the sex difference in neonatal postural asymmetry observed in 1-day-old rat pups by both Ross, Glick, and Meilbach (1981) and Rosen, Berrebi, Yutzey, and Denenberg (1983); (b) the sex difference in rotational direction selected by adult rats described by Glick and Ross (1981); or (c) the sex difference in paw preference in a reaching task reported by Collins (1975) in house mice. However, in the course of these unsuccessful studies, we did notice an apparent difference between male and female gerbils in their use of right and left forepaws when standing immobile in the species-typical tripodal stance (see Figure 1).

In a tripodal stance, male gerbils were more likely than were females to rest on their right forepaws and to hold their left forepaws in the air. Regardless of sex, gerbils from 2M IUPs were more likely than were gerbils from 2F IUPs to rest on their right forepaws (Clark, Robertson, & Galef, 1993).

The results of further experiments were consistent with the hypothesis that perinatal exposure to gonadal hormones played a role in development of asymmetry in the tripodal stance of Mongolian gerbils. We found that, as adults, female gerbils that we had injected with low levels of T in the days immediately following their birth were more likely to use their right forelimbs for support when in the tripodal stance (the male pattern) than were control females that we had injected with vehicle. On the other hand, and unexpectedly, male gerbils we injected shortly after birth with low levels of T, as adults, rested on their left forepaws (the female pattern)

FIGURE 1   Drawing from a photograph of a young adult male gerbil resting on its right forepaw, the male pattern of the tripodal stance.

more frequently than did control subjects injected with oil (Clark, Robertson, & Galef, 1996).

The experimental findings, like those of an earlier report of effects of hormonal manipulations on tail posture in female (but not in male) rats (Rosen et al., 1983), demonstrated effects of perinatal administration of T on behavioral lateralization. Such results are consistent with a larger body of correlational evidence (see Bradshaw & Rogers, 1993; James, 1988; Rogers, 1989, for reviews) that, as Geschwind and Galaburda (1987) hypothesized, implicates T in the development of lateral asymmetries. On the other hand, the direction of the effects we and Rosen et al. (1983) observed were not always consistent with expectations based on the Geschwind and Galaburda (1987) hypothesis. For example, we found that exposing neonatal gerbils to exogenous T increased expression of the female pattern of forepaw use by males and either masculinized or left unaffected the pattern of forepaw use by females, with large doses of T having less effect than small ones (Clark et al., 1996).

EFFECTS OF PERINATAL STRESS ON ADULT REPRODUCTION

The experiments described here demonstrate that experiences of rodents during the perinatal period, especially their prenatal exposure to steroid hormones originating in their uterine neighbors, can have important effects on adult morphology and behavior. Of course, it has been known for some time that variables other than IUP can affect levels of fetal exposure to exogenous gonadal hormones and, consequently, can influence the probability of expression of hormone-sensitive characteristics in adult mammals. In particular, stress applied to pregnant rodents has been shown to affect many of the same anatomical, physiological, and behavioral traits affected by IUP. Age at vaginal opening, length of estrus cycle, and litter sex ratios are all greater in daughters of stressed than unstressed females, and daughters of

stressed dams are both less fertile and less fecund than are daughters of unstressed dams (Herrenkohl, 1979; Herrenkohl & Politch, 1978; Kinsley & Svare, 1988; Politch & Herrenkohl, 1984; Ward & Weisz, 1980). Similarly, daughters born to pregnant mice housed at high densities (a potential social stressor) have greater anogenital distances and reduced copulatory receptivity relative to uncrowded control mice (Allen & Haggett, 1977; Zielinski, Vandenbergh, & Montano, 1991).

Sons of stressed rat dams, like their sisters, show effects of the stressors applied to their mothers. Sons of stressed dams are less willing to copulate with females in estrus than are sons of unstressed dams (Ward, 1971). This impairment in the sexual behavior of sons of stressed dams is believed to reflect a shift away from a sensitive period for central nervous system development in the age at which sons of stressed dams experience a species-typical surge in circulating levels of T (Ward & Weisz, 1980).

Given the apparent hormonal basis of effects of both IUP and stress on adult phenotypes, it is not surprising to find also that effects of stressors and IUP interact. For example, vom Saal et al. (1990) reported that stress applied to mice during the last week of their pregnancies results in (a) higher circulating levels of T in both male and female mouse fetuses, and (b) increases in anogenital distance and estrus cycle lengths in 2F, but not in 2M, female mice.

CONCLUSIONS

More than a century ago, Darwin focused attention on the quantitative variation in both morphological and behavioral characteristics to be observed in members of any natural population. Elucidating the mechanisms responsible for such individual differences in phenotype is one of the basic tasks of developmental neuropsychology and psychobiology.

Although we know today that naturally occurring phenotypic variability has both genetic and environmental causes, recent advances in molecular biology have led to an ever-increasing focus on genotype as a source of this variability. Results such as those described here make clear that naturally occurring variation in perinatal experience has effects on adult morphology and behavior that can be as important as those produced by the expression of alternative alleles found in natural populations.

Although there is, as yet, relatively little relevant data, it seems reasonable to suppose that normally occurring variation in perinatal exposure to gonadal hormones can affect temperament and life-history strategy in members of our species as well as others (Udry, Morris, & Kovenock, 1995). Consequently, studies of the effects of normal variation in hormonal exposure caused by gestation in different IUPs in the uteri of litter-bearing rodents may provide more than basic information

about sources of phenotypic variability in litter-bearing mammals. Such studies may also provide a useful model system in which to explore the role of normal variation in perinatal exposure to gonadal hormones in producing variation in the morphology and behavior of adult *Homo sapiens*.

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