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Contiguity to Males in Utero Affects Avoidance Responding in Adult Female Mice

Abstract. *Female mice that had been situated in utero between two female fetuses displayed higher levels of active avoidance responding in adult life than females that had been located between two male fetuses and males for whom uterine position was without effect. Uterine position, therefore, influences acquired as well as species-typical behaviors.*

Clemens and co-workers (*1*) discovered that the position of the female rat fetus relative to its male siblings affects both its morphology and adult behavior. This seminal work and the subsequent efforts of others (*2*) studying rats and mice revealed that females located in utero between two males (mFm) have lengthened anogenital distances at birth and show more male-like copulatory and aggressive behavior than females not so situated. Such mFm animals are also less sexually attractive, have longer estrous cycles, attain puberty later, and become anovulatory earlier in response to postnatal testosterone challenge (*3*). That the effects of male contiguity can be generally classified as masculinizing, that perinatal exposure to testosterone yields similar effects, and that the fetal testis secretes androgens (*4*) have led to the view that the influence of contiguity is mediated, in some manner, by the transfer of testicular androgen from the fetal males to the female (*1, 2*).

Specification of the influence of uterine position on behavior addresses the issue of the genesis of individual differences in the display of behavior, especially behaviors dependent on particular concentrations of gonadal steroids. However, the behaviors thus far examined have not extended beyond the species-typical, unlearned, variety. The existence of gender differences in the display of various acquired behaviors (*5*) underscores the need to determine whether the uterine environment modulates the display of such behaviors. We have considered this issue and now report that uterine position significantly influences an acquired behavior, active avoidance responding.

Nulliparous Rockland Swiss albino mice (60 to 70 days old) (*6*), kept in groups with males, were housed singly upon the discovery of copulatory plugs which signified day 0 of pregnancy. The animals were kept in translucent cages (11 by 7 by 5 inches) containing pine shavings, provided with food and water in excess, and maintained on a cycle of 12 hours of light and 12 hours darkness with lights on at 0600 hours. On day 18 of pregnancy, 1 day prior to term, each animal was anesthetized with ether, the uterus exposed, and the fetuses expelled. They were placed on absorbant toweling in the order found in each uterine horn, cleaned with saline, and kept warm. Upon becoming motile and attaining the pink-red coloration characteristic of the full-term newborn, they were sexed and the following four groups of eight animals formed: (i) females located in utero between two males (mFm); (ii) females between two females (fFf); (iii) males between two males (mMm); and (iv) males between two females (fMf) (*7*). Each subject was fostered to a lactating animal that had delivered within the previous 24 hours and had been allowed to retain four pups of the sex opposite to that of the experimental animal, thus permitting us to identify the experimental animals at weaning.

Weaning was on day 21 and each of the 32 mice was housed with a like-sex and ear-punched conspecific. This arrangement was maintained throughout the experiment to obviate the potential confounding influence of long-term isolation. On day 60, each animal was placed into the testing apparatus (*8*) for a 30-minute habituation period followed by a single shaping session. They were trained by the method of successive approximations to terminate, by pressing a lever, a 0.25-mA scrambled electric shock delivered to the paws through the stainless steel grid floor (*9*). At the onset of the electric shock the houselights (three 4.75-W bulbs) were turned on, and the same lever that terminated the shock turned off the lights. If a response did not occur within 2 minutes, both the shock and the houselights were extinguished. The interval between each presentation of shock was 15 seconds. All subjects learned to escape, the criterion for which was ten successive escape responses in the absence of experimenter intervention.

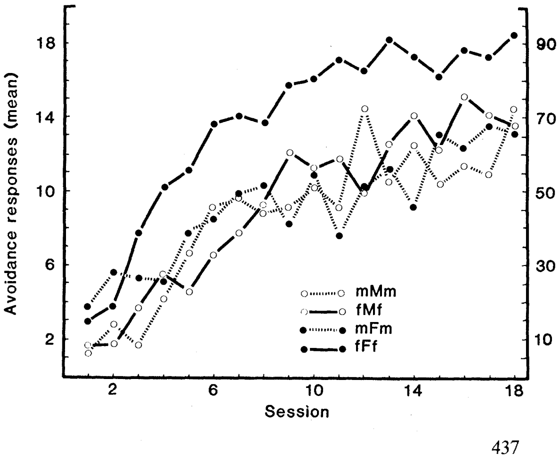

Fig. 1. Mean number and percentage of active avoidance responses made by adult female mice located in utero between two female fetuses (*fFf*) and two male fetuses (*mFm*) and males located between two females (*fMf*) and two males (*mMm*). Eight animals were assigned to each group. Twenty trials were given on each of the 18 test sessions.

Test sessions, beginning on day 61, were similar to the training session except that an avoidance contingency was added and the interval between trials increased to 60 seconds. A trial began with a 10-second warning period signaled by the onset of the houselights. If the mouse pressed the lever during the warning period the houselights were turned off and shock was not presented. If a response did not occur, the lights remained on and shock was delivered. Both the shock and lights were terminated as soon as the animal pressed the lever or after 1 minute. Twenty trials were given during each of 18 sessions (*10*) which were held between 0900 and 1400 hours. The number and latency of avoidance responses were recorded (*11*).

The results are presented in Fig. 1. An analysis of variance yielded a significant group effect [$F(3, 28) = 6.04$, $P < .003$] which, as shown in Fig. 1 and verified by post hoc analyses (*12*), is accounted for by the enhanced avoidance responding of fFf mice. The level of responding of mFm subjects was similar to that of males (mMm and fMf), for whom uterine position was without effect. As expected, all groups of animals increased their scores across sessions [$F(17, 476) = 2.68$, $P < .01$] (*13*). The group by session interaction was not significant, indicating that the rate of acquisition was similar for all groups and that uterine position influenced performance. It is possible, however, that had additional sessions been given the scores of groups mFm, mMm, and fMf would have reached that of fFf. The groups did not differ in their response latencies after onset of the warning signal or in their anticipatory responses, that is, lever pressing in the interval between trials.

It has been shown that female rats outperform males on various avoidance tasks (*14*) and that prenatal androgen is responsible for this difference (*15*). An overall gender difference in the direction of female superiority was found in our experiment when the data from mice of each sex were pooled across the uterine position variable [$F(1, 30) = 4.54$, $P < .05$]. We therefore conclude that the influence of male contiguity on the active avoidance responding of female mice is one of masculinization, apparently caused by stimulation of female fetuses by testicular androgen. Our findings demonstrate the efficacy of contiguity to two males, but we did not test females that had been located in utero between a male and a female (mFf). Previous research dealing with species-typical behavior, if applicable here, suggests that the avoidance behavior of mFf mice would be intermediate between that of males (fMf and mMm) and fFf females.

Our findings, and those of others (*1–3*), lead to an important question concerning polytocous mammalian species, those for which each pregnancy typically results in the birth of more than two offspring: What constitutes a "true" female? Is it any mammal possessing the XX genotype or only an animal with the XX genotype that has not been "contaminated" during fetal development by contiguous male siblings? This question requires consideration in assessments of the role of gender on those behavioral and physiological indices for which gonadal steroid hormones have been implicated.

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6. Rockland Swiss albino mice, bred in our facility, were kept as an outbred strain in a closed colony.
7. A total of 27 animals donated the 32 subjects. Five donors each provided two pups.
8. The apparatus (19 by 19 by 18 cm high) was constructed of clear Plexiglas. The lever, which operated with a force of 9 g, was centrally positioned on one wall, 10 mm above the floor, and protruding 15 mm into the chamber. The apparatus was housed in a sound-attenuating compartment.
9. Discontinuous shock sequences (0.5 second on, 0.5 second off) were used to facilitate the acquisition of avoidance behavior [M. R. D'Amato, D. M. Keller, L. DiCara, *J. Comp. Physiol. Psychol.* **58**, 344 (1964)].
10. The test session schedule was six consecutive days of testing followed by 1 day off and three periods of four consecutive tests each followed by 1 day off.
11. The operation of the apparatus as well as data collection were performed automatically by a microprocessing computer, thus virtually eliminating the possibility of experimenter bias.
12. Duncan's test with α set at 0.01 [G. Keppel, *Design and Analysis: A Researcher's Handbook* (Prentice Hall, Englewood Cliffs, N.J., 1973)].
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Plasticity of Motor Behavior in Monkeys with Crossed Forelimb Nerves

Abstract. *Monkeys in which nerves innervating the flexor muscles of the forearm and hand (the ulnar or the median nerve) had been surgically cross-united with the nerve innervating the extensor muscles (the radial nerve), and vice versa, showed excellent (ulnar-radial crosses) to moderate (median-radial crosses) control of movement performance after regeneration. Antagonistic movement responses were seen occasionally, but these were corrected almost immediately. Stimulation of the crossed nerves showed that they had innervated the antagonistic muscle groups. The results reveal the capacity of the primate central nervous system to adapt to gross disturbances imposed on the execution of movements by changes in peripheral innervation.*

Nonprimate species such as rats or cats either do not adapt or adapt poorly to cross-union of flexor and extensor nerves and to muscle or tendon transposition (*1, 2*). Nonhuman primates seem to adapt better to nerve cross, but use "tricks" (*3*). Humans, however, can learn to use once-denervated muscles now supplied by a foreign nerve (*4*) and to adapt to muscle transposition (*1, 5*). We have found that, like humans, monkeys can adapt to major rearrangements in peripheral innervation of antagonistic muscle groups, after cross-union of flexor and extensor nerves of the distal forelimb.

Flexor muscles of the monkey and human forearm and hand are innervated by the median and ulnar nerves, and extensor muscles by the radial nerve (*6*). Eleven young Java monkeys (crab-eating macaque, *Macaca fascicularis* ssp.), all born and bred in the laboratory, were studied. Five received cross-anastomosis of the ulnar and radial nerves (U-R group), and the other six, of the median