Prenatal Hormone Exposure and Sexual Variation

Hormone exposure in the womb is instrumental in shaping the sexual anatomy, physiology and behavior of mammals

John G. Vandenbergh

How is an individual's sex determined? In high school biology class you probably learned a basic rule for mammals: Individuals with one X and one Y chromosome develop into males. Those with two X's develop into females. Distinguishing between the resulting males and females should be straightforward. Unfortunately for those who like simple rules, the story is far more complex.

X and Y chromosomes are only the beginning of sex determination. Biologists have recently taken a closer look at the events between fertilization and sexual maturity that establish an individual's sexual characteristics. These events help explain variability among individuals in sexual anatomy, physiology and behavior. For example, an XX individual can exhibit some masculine traits if hormone production or sensitivity is abnormal during early development.

In fact, there is almost a continuum of sexual traits between male and female. The ability of environmental influences during development to produce such a continuum demonstrates that another classical dichotomy, between nature and nurture, is in fact a synergy: Genes and environment work together to produce an organism. Specific genes are only turned on when the environment of the cell, tissue, organ or organism calls for them. In the case of sexual characteristics, one mechanism by which environmental variables exert their influence is through the activity of hormones.

Hormones are substances released by cells into the bloodstream, where they travel throughout the body and influence the function of other, distant cells. Hormone molecules themselves, or the enzymes that produce those molecules, are encoded by the genome, but hormone concentrations can be modulated by a wide array of environmental factors, including stress, food consumption, temperature, and time of year. In turn, hormone concentrations modulate the expression of genes in a variety of different cell and tissue types, producing anatomical, physiological and behavioral differences.

My own studies in rodents have helped show how hormones affect development in the womb, producing differences that later manifest themselves in adult morphology, physiology and sex-related behavior. A detailed understanding of the sensitivity of the fetus to hormones will play an important role in the evaluation of the controversial impact of hormone-mimicking environmental substances on animal and human health and development.

Hormones and Sexual Development

Of course, sex hormones exert a powerful effect at the time of puberty. Anyone who has watched a puppy develop into an adult dog has noted the decline in slipper chewing behavior and the increase in interest in the opposite sex. In males, androgens such as testosterone act at puberty to sculpt the body into its adult shape and produce male physiology and behavior. In females, high levels of the gonadal hormones estrogen and progesterone at puberty result in characteristically female adult body shape, physiology and behavior.

Puberty is the only period of female development that is characterized by a large surge in gonadal hormone activity. In contrast, males experience two surges in testosterone concentration. The first begins during fetal development. In the laboratory mouse, the fetal testes begin to produce testosterone midway through gestation, on the 11th or 12th day after conception. The male fetus is exposed to a relatively high concentration of testosterone until 4 or 5 days after birth. Testosterone levels then plummet, and remain low for about two months, rising sharply again at the time of puberty *(Figure 2)*.

The high level of testosterone present in the male during the period before and just after birth has major consequences. If denied exposure to this male hormone, either through fetal surgery to remove the testes, or through pharmacological agents that block the normal response to testosterone, the male develops anatomically, physiologically and behaviorally as a female.

Intrauterine Position Effect

In the early 1970s biologists working on neurotransmitters in the rat brain discovered that hormone levels during fetal development are also important in the establishment of variation between members of the same sex. Lynwood Clemens and his laboratory group at Michigan State University routinely distinguished newborn male and female rat pups based on the distance between the anus and the genitals. Males have a longer anogenital distance than females.

Graduate student Linda Coniglio noticed that some female rats had longer anogenital distances than others. She reported her discovery to

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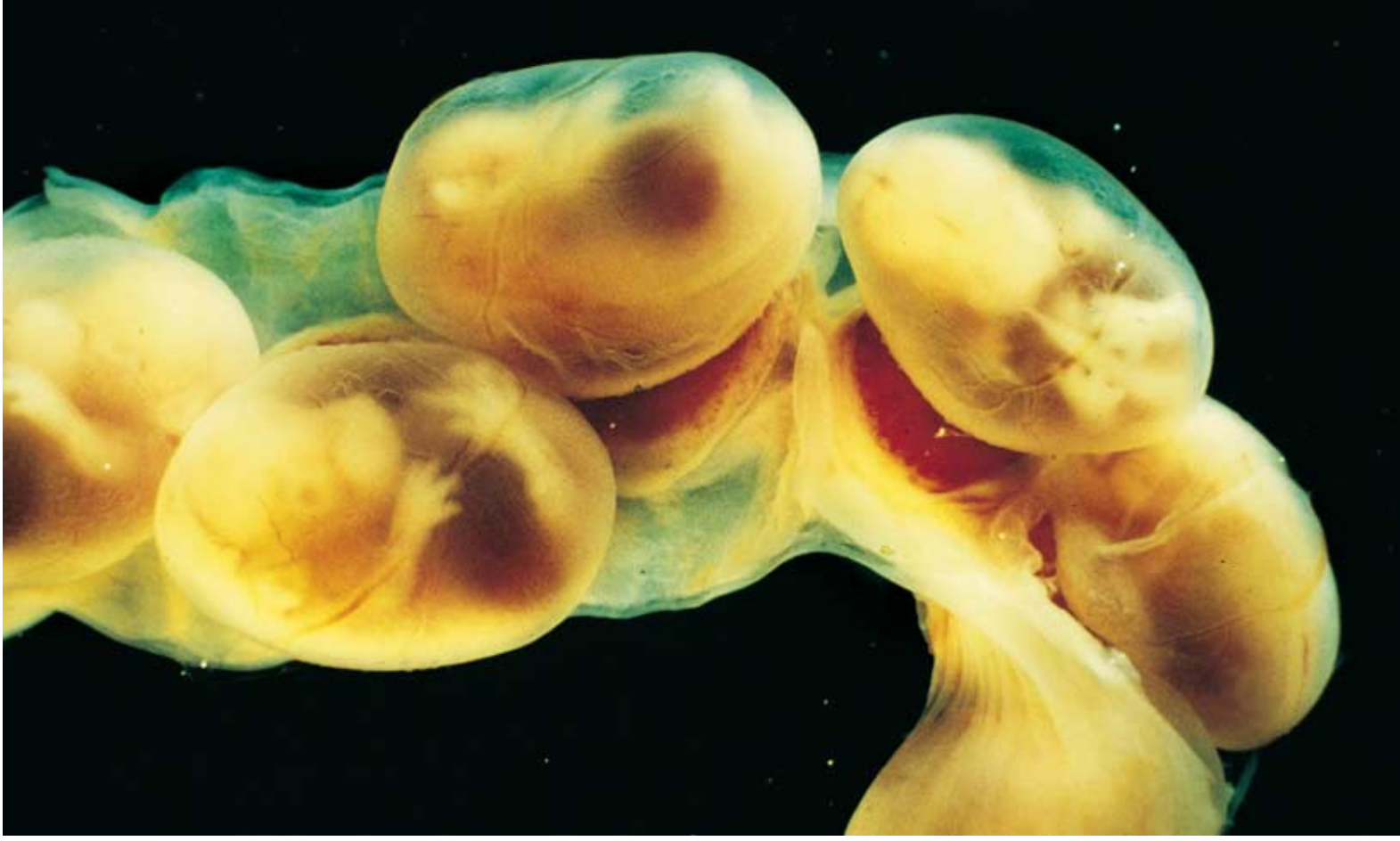

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Figure 1. Mouse fetuses develop lined up in the horns of the mother's uterus. Mammalian fetuses are exposed to hormones and hormone mimics from a variety of sources. Hormones may be released into the womb by neighboring littermates, and hormones produced by the mother or hormone mimics from external, environmental sources may enter the embryos through the mother's circulatory system. Exposure to these substances has major consequences for later development and behavior.

Clemens, and they began to investigate potential causes of this variation. Delivering the rat pups by Caesarean section revealed a correlation: Females that developed in close proximity to male littermates had longer anogenital distances *(Figure 4)*. Thus the variability appeared to result from differences in the prenatal environment experienced by the pups.

Since testosterone and other steroid hormones can move through cell membranes readily, it seemed likely that this *intrauterine position* (IUP) effect was a result of the diffusion of testosterone from male siblings to their female littermates while in the womb. In fact, anogenital distance is a function of testosterone concentration: The higher the testosterone concentration that a female fetus is exposed to, the longer the anogenital distance of the resulting pup. So, the more males in proximity to a given female, the more masculine characteristics that female displays.

Following the original discovery of the intrauterine position effect in rats, Frederick vom Saal at the University of Missouri and his colleagues have pursued the phenomenon in considerable detail in the laboratory mouse. The mouse makes a good subject for this work because many strains produce large litters and because the fetuses are lined up like peas in a pod in the two horns of the mouse uterus. A female located between two males is designated as a 2M female, and a female without a male on either side is designated as a 0M *(Figure 3)*. Approximately sixty percent of the females have a male on one side (1M) and the remainder are divided more or less equally between the 2M and 0M conditions.

Similar categories can be established for male exposure to female proximity, but this, at least in the mouse, seems to have considerably fewer long-term consequences. vom Saal and his colleagues confirmed the original findings in rats that proximity to a male during fetal development results in an elongated anogenital distance in females. The intrauterine position effect has also been demonstrated in the gerbil by Mertice Clark and colleagues at McMaster University in Canada.

The anogenital distance has become a useful measure of prenatal masculinization and, when adjusted for body weight, provides an index, called the Anogenital Distance Index (AGDI), indicating the amount of testosterone exposure during fetal development. In early studies, the location of male and female fetuses relative to each other had to be determined by Caesarean section. Now, using this index, a relatively accurate prediction can be made after a natural vaginal delivery about the proximity of males to a particular female in the uterus.

IUP, Physiology, and Behavior

Armed with this easy way of estimating testosterone exposure in female newborns, biologists have begun to assess the effects of this exposure on a variety of traits. One place where they have looked is the brain of the rat. In the early 1990's, Kenneth Faber and Claude Hughes at Duke University found that specialized regions of the brain vary in size as a function of a female's proximity to males during fetal development. Portions of the

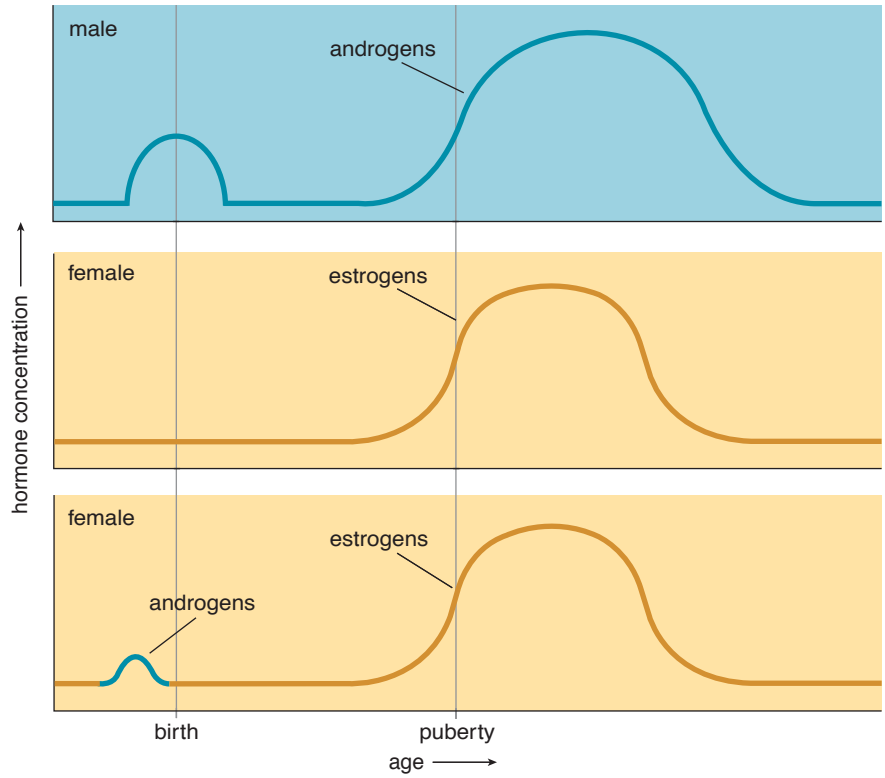

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Figure 2. Male mice experience two spikes in hormone production: one that begins during fetal development and another at puberty *(top)*. The fetal testes begin to produce testosterone 11 or 12 days after conception, and continue to do so until 4 or 5 days after birth. In contrast, females normally experience only the second, pubertal increase in estrogen concentrations *(middle)*. However, androgens from male littermates in the womb can diffuse into their sisters' bloodstreams and influence their development *(bottom)*.

hypothalamus are sexually dimorphic and seem to be important in controlling mating behavior. These areas are larger in males than in females, but there is size variation between females. This variation is correlated with anogenital distance, and thus with testosterone levels during development.

The physiological characteristics of females are also permanently altered as a result of exposure to naturally high levels of testosterone from their male neighbors in the womb. Testosterone concentrations are slightly elevated in 2M females, and these females are more sensitive to testosterone than 0M females. When treated with testosterone as adults, they show greater changes in physiology and behavior. In addition, 2M females are slightly masculinized in a variety of other physiological characteristics. Among mammals, the age at puberty is typically later in males than in females; as expected, puberty in 2M females is slightly delayed compared to 0M females. Another major difference between male and female mammals is that females have ovarian cycles and males are acyclic. Females from the 2M position not only start cycling later but show a more irregular ovarian cycle than those from a 0M position. Females from the 2M position are more masculine than their sisters, but they are functional females who ovulate, mate and give birth to normal-sized litters.

Given the effects of intrauterine position on brain morphology and on physiology, it comes as little surprise that IUP also affects mating preferences and behavior. A male mouse allowed to choose between a 0M and a 2M female more often chooses the 0M female. If he does choose to mate with the 2M female, the female assumes a somewhat abnormal mating posture, which tends to result in less successful mating. Not only is the 2M female less attractive to males than the 0M female, she more frequently mounts other females when given an opportunity. 2M females show a higher level of aggressive behavior and are more likely to be novelty seeking than 0M females. Thus, a wide array of behaviors including attractiveness, mating posture, mounting behavior and aggression are all at least partly influenced by being adjacent to males in the uterus.

IUP in Natural Populations

The anatomical, physiological and behavioral effects of IUP in the laboratory suggest that exposure to hormones in the womb may influence adult survival and reproduction in wild populations. For example, higher levels of aggression in 2M females should allow those females to survive and reproduce better under crowded conditions, because these females should be better at defending their territories against intruders. In contrast, under more favorable conditions, 2M females should not be as successful at producing pups because they reach puberty later and are less attractive to males.

In order to test these hypotheses, vom Saal and I decided to take advantage of the seemingly endless highway construction around Raleigh, North Carolina, near my laboratory. The "beltline" around the city includes a number of cloverleaf-shaped highway exchanges. In addition to their intended function of keeping traffic moving, these cloverleafs turned out to be useful to us as large outdoor mouse enclosures. A relatively large population of mice can live within one quadrant of the interchange, and the mice are relatively unsuccessful at entering or leaving these "highway islands" because of the expanse of road they must cross.

My postdoctoral associate, William Zielinski and I collaborated with vom Saal on this experiment to obtain a large number of animals from known intrauterine positions. Each laboratory did half of the Caesarean sections, and vom Saal flew his mice from Missouri to North Carolina in his own airplane. The native population of rodents on a highway island approximately one hectare in size was trapped and released elsewhere. We then released about twenty 0M females and twenty 2M females onto the island. Along with the females, we released forty male mice of the known 1F position. The resulting population of mice was at the upper end of densities seen on comparable islands, resulting in slightly crowded conditions.

Each evening we opened small metal box traps and baited them with peanut butter and rolled oats, and each morning we checked the traps for captured animals. The traps were laid out in a grid, so that we could assess the home ranges of individual animals. The mice were individually marked so that if we

repeatedly caught the same individuals, we could track their location and physical condition. We were also able to determine whether the females were in the late stages of pregnancy or were lactating. The highway island experiment was run twice, once in the fall of 1989 and once in the spring of 1990.

We found that the 2M females occupied 40 percent larger home range areas than the 0M females. In fact, in the spring, 2M females had home ranges about as big as those of males *(Figure 7)*. 0M females were somewhat more successful at reproducing, but this difference was not statistically significant. These results were consistent with our expectation that wild 2M females are more aggressive in maintaining a home range and perhaps less successful in breeding than the 0M animals.

Despite the rather high densities of mice used in this experiment, 2M females did not show higher survival, suggesting that they may not be at an advantage under crowded conditions. However, our results do suggest that a 2M female should be more likely to succeed in a harsh environment where a larger territory is needed, or in an environment in which she is a recent immigrant who must establish and defend a new territory. A 0M female, on the other hand, may have an advantage in a resource rich environment because of her ability to produce pups earlier. Thus, differences induced by prenatal hormone exposure may help to explain variability within populations in the manner in which mice, and perhaps other small rodents, adapt to their environments.

Prenatal hormone levels might affect population characteristics in small mammals via a number of other mechanisms. For example, crowding and stress cause pregnant females to produce higher levels of testosterone, resulting in more masculinized pups. The resulting daughters resemble 2M females, regardless of their position in the womb, and thus may have lower reproductive success. 2M females or masculinized females are more likely to emigrate. Increased testosterone levels in crowded mothers thus cause them to produce daughters who are more likely to leave the crowded environment in which they are born.

Female masculinization also alters the sex ratio of offspring produced. 2M females produce more male offspring (58 percent male, 42 percent female),

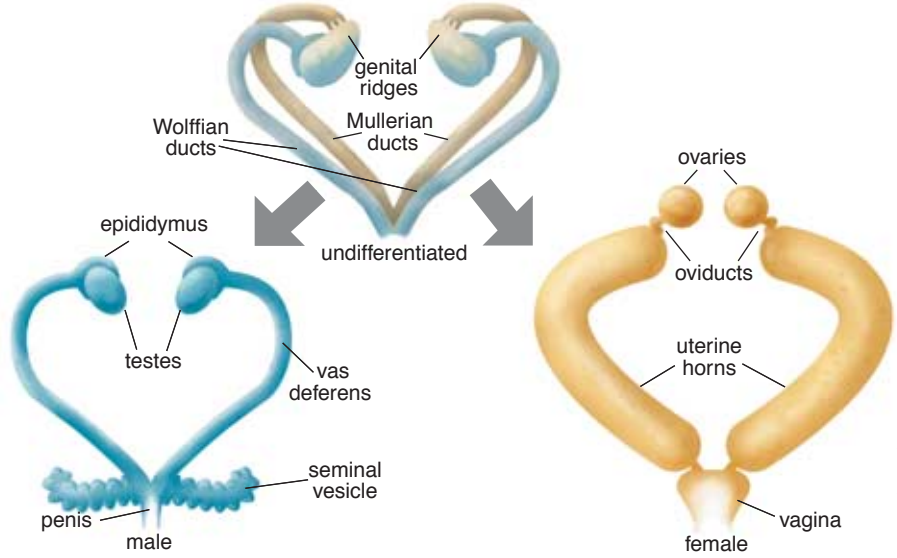

Figure 3. Mouse reproductive anatomy begins to develop ten or 11 days after conception. As shown in this schematic drawing, the precursors of both the male and female internal organs (Wolffian and Mullerian duct systems respectively) are present at first. In males, the undifferentiated genital ridges develop into testes around day 12 and produce hormones that cause the regression of the Mullerian ducts and the differentiation of the Wolffian ducts into the vas deferens and seminal vesicles. In females, the ovaries differentiate slightly later in development. In the absence of male hormones, the Mullerian ducts develop into the uterus and oviducts.

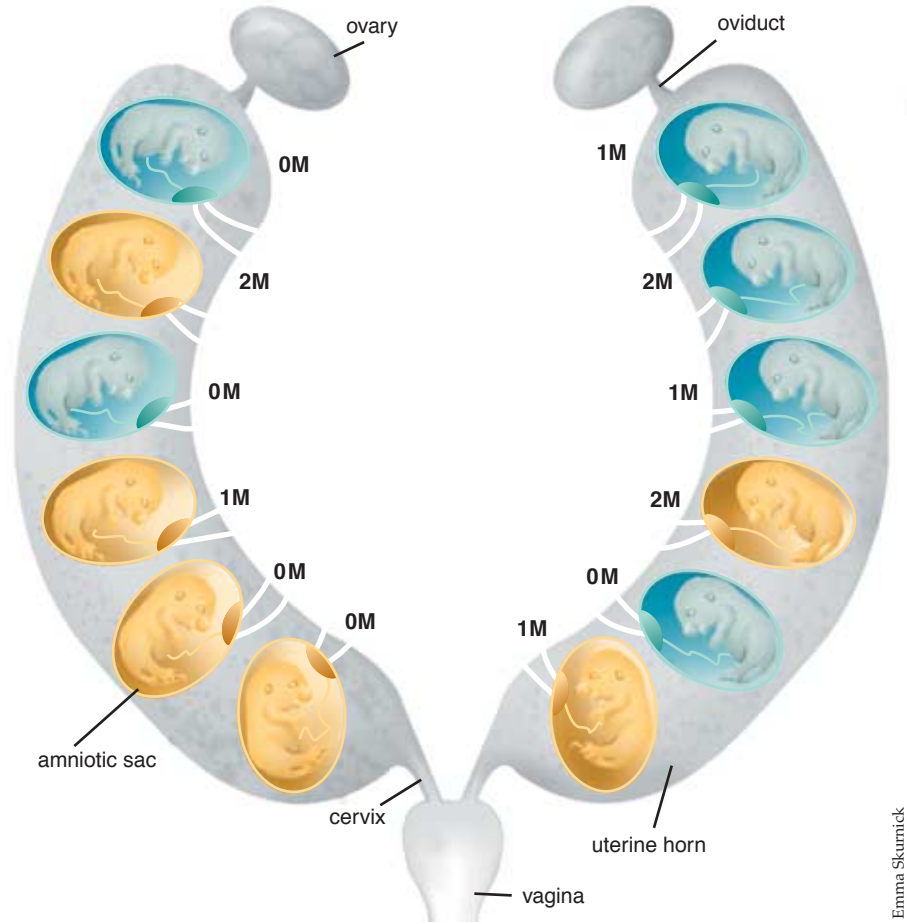

Figure 4. In many small mammals that give birth to large litters, male *(blue)* and female *(orange)* fetuses are lined up in the uterus like peas in a pod. In mice, a system has been developed to describe each fetus's intrauterine position. A fetus with a male on either side is designated 2M, one with a male on only one side is 1M, and one with no male neighbors is 0M.

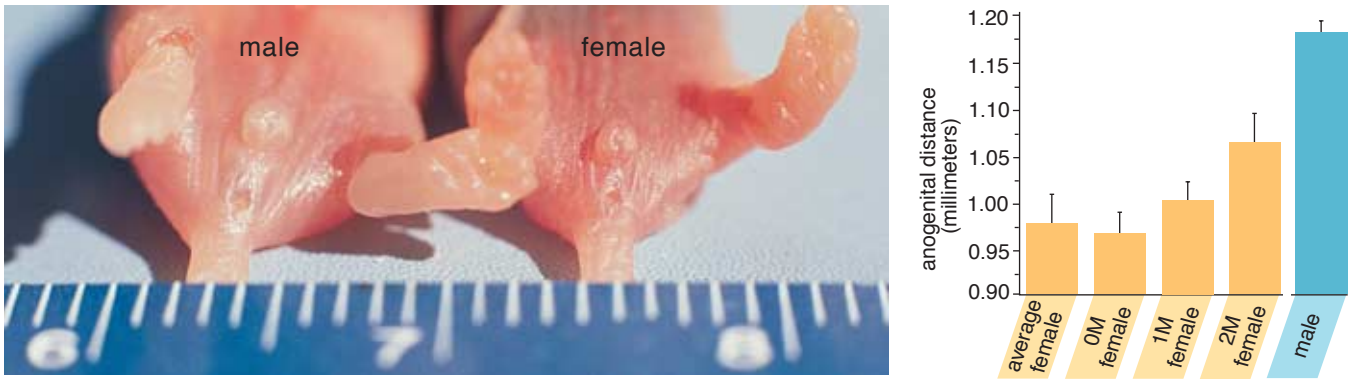

Figure 5. Male mouse pups have a longer distance between the anus and genitals than females *(left)*. Variation in anogenital distance among females is correlated with intrauterine position *(right)*: 2M females have the longest anogenital distances, 0M females have the shortest, and 1M females are intermediate. (Photograph and data provided by the author.)

while 0M females produce more female offspring (42 percent male, 58 percent female). Crowding, therefore, might result in a runaway process where an excess of males are produced. Crowded females produce masculinized daughters who then produce more sons. The daughters in these male-biased litters are in turn more likely to have had male neighbors in the womb; as a result, they too produce more male offspring. This might cause a shortage of females, and thus a shortage of pups, which could lead to a crash in population size. In fact, the effects of intrauterine hormone exposure have been suggested as a possible mechanism for large-scale fluctuations in population size in small mammals such as voles, lemmings and snowshoe hares that are famous for their periodic population booms and busts.

It is unclear why or how masculinized mothers produce more sons, or exactly how this effect might be used to modify sex ratios at the population level. The laboratory animals most often used to investigate the effects of hormones on development do not usually undergo regular population cycles, although they do experience periodic population explosions. Much more research is needed to confirm the role of hormonal effects in population regulation, but it is interesting to speculate.

Endocrine Disruptors

The environment of the mother clearly influences a variety of sexual characteristics indirectly through endogenous hormones in the womb. Pregnant females are also constantly exposed to compounds in their environment that mimic or interfere with these endogenous hormones. Concern about the impact of man-made chemicals on development began to emerge in the 1950s and '60s with the realization that pesticides such as DDT caused eggshell thinning and other developmental abnormalities in birds. Many of these chemicals interfere with the endocrine system. The term "endocrine disruptor" has been coined to refer to a compound that either mimics or blocks the action of natural hormones.

Many endocrine disruptors are man-made compounds such as pesticides, plastics and industrial chemicals, but some, such as phytoestrogens, occur in plants. Most of the known disruptors act upon the production of estrogen or the ability of cells to respond to estrogen. There are fewer compounds known to interfere with the production and function of male hormones. Endocrine disruptors have been implicated in reproductive problems in a wide array of animals from marine snails to alligators to people. But proving that these problems are a result of endocrine disruption is not a simple matter, and so these claims remain controversial.

In another collaboration with vom Saal's laboratory, we have found that intrauterine position influences an individual's response to endocrine disruptors. Bisphenol A is an estrogen mimic found in the lining of food and beverage containers and in dental resins. It leaches from these materials into human food as well as into the natural environment. We fed bisphenol A to pregnant female mice from day 11 to 17 of gestation. Pups were then delivered by Caesarian section to identify their intrauterine positions. We found that bisphenol A accelerates the onset of puberty more substantially in 0M females compared to 2M females, with

	trait	0M female	1M female	2M female	male
morphology	anogenital distance	short			long
	volume of sexually dimorphic nucleus of hypothalamus	small			large
physiology	fetal testosterone level	low			high
	onset of puberty	early			late
	production of male pups	42%		58%	
	timing of pregnancy	early		late	
	sensitivity to testosterone	low		high	
	sensitivity to bisphenol A	high		low	
behavior	aggressiveness	less			more
	home range size	small			large
	likelihood of mounting other females	low		high	

Figure 6. Intrauterine position affects a wide variety of anatomical, physiological and behavioral traits in small rodents. In general, increased exposure to male littermates is associated with expression of more masculine traits in females. (Adapted from Ryan and Vandenbergh 2002).

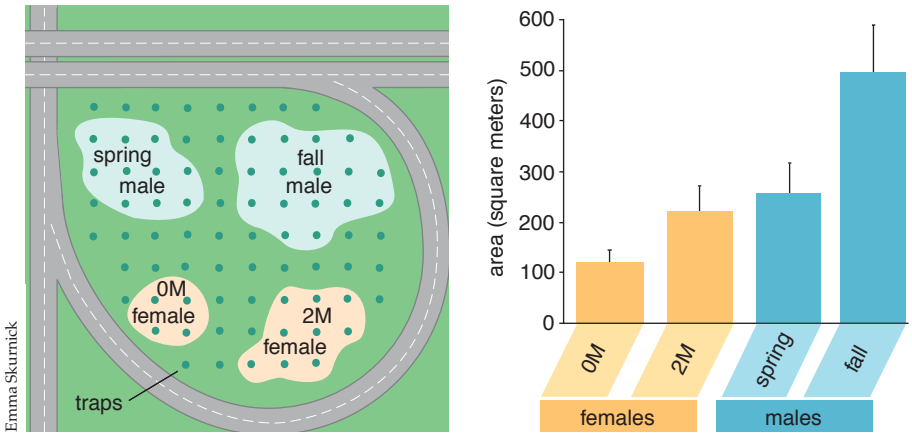

Figure 7. In 1989 and 1990, the author and colleagues tested the effects of intrauterine position in the field by placing experimental populations of mice on a "highway island" created by a cloverleaf interchange *(left)*. Twenty 2M females, 20 0M females and 40 males were released onto the island and monitored by daily trapping. 2M females had home ranges 40 percent larger than those of 0M females, and comparable to those of males in the spring. (Data from Zielinski *et al.* 1992.)

1M females showing an intermediate response *(Figure 9)*. These results indicate that environmental endocrine disruptors and natural prenatal hormone exposure may interact to alter reproductive physiology.

Work on intrauterine position has clearly shown that prenatal hormone exposure affects behavior later in life. Endocrine disruptors that alter prenatal hormone levels are also expected to influence behavior. Members of my laboratory group confirmed this hypothesis by showing that prenatal treatment with an endocrine disruptor that blocks testosterone function causes changes in juvenile play behavior.

Male and female mammals play at different rates and express different postures during play. Play is one of the few sexually dimorphic behaviors expressed when gonadal hormone concentrations are low. Most animals show a decided increase in play behavior during the juvenile period, which fades away at the time of puberty when the gonadal hormone concentrations go up. It is the presence or absence of testosterone during fetal development that determines an individual's play behavior. Male rats that are naturally exposed to testosterone during fetal development show characteristically male rough-and-tumble play behavior as juveniles. If denied exposure to testosterone through pharmacological manipulations, the male rats play like females. Similarly, if female fetuses are exposed to testosterone they show male-like play behavior as juveniles.

To carry these findings into the world of endocrine disruptors, one of my students, Andrew Hotchkiss, injected pregnant female rats with the anti-androgen vinclozolin. Vinclozolin was used to control fungal growth on fruit crops beginning in the mid 1970s. Its use is now being phased out in the United States due to its endocrine-disrupting effects. Vinclozolin blocks the response to testosterone by interfering with testosterone receptors.

Hotchkiss and collaborators in the laboratory of Earl Gray at the US Environmental Protection Agency studied play behavior in the pups produced by females who had been injected with vinclozolin during pregnancy. Upon weaning, Hotchkiss placed pairs of brothers in cages together until they were 35-days old. He then separated the two cage-mates overnight and reunited them the next morning. After this period of separation, the cage-mates typically show an enhanced period of greeting and play. Hotchkiss found that males treated with vinclozolin prenatally showed reduced levels of play, similar to those of normal females. Females treated with testosterone increased their rough-and-tumble play behavior to a level significantly higher than untreated females *(Figure 10)*.

Studies in my laboratory demonstrate how endocrine disruptors found in plastics and fungicides can influence reproductive physiology and behavior in rodents. More and more studies are implicating endocrine disruptors in causing changes in the anatomy, physiology and behavior of people and wildlife. In 1998 the EPA identified 87,000 chemical compounds that need to be screened for endocrine disrupting activity. The problem is that compounds with endocrine disrupting activity are difficult to identify on the basis of chemical structure: For reasons that are not well understood, they often don't look anything like the hormones or hormone receptors that they affect. Testing the chemicals on animals in the laboratory is the best way to determine whether they have endocrine-disrupting activity, but these tests are expensive and time consuming.

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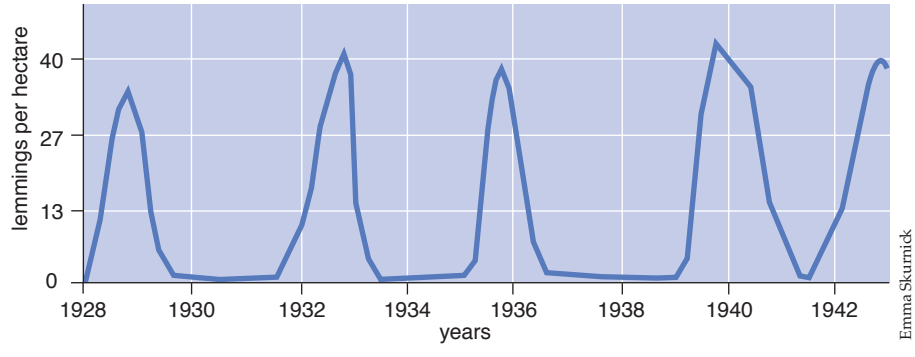

Figure 8. Lemmings are well known for their cyclical population booms and busts (shown here from data collected near Churchill, Manitoba). The effects of intrauterine position and crowding stress on the sex ratio of litters produced are possible mechanisms of population fluctuations in small mammals. Crowded females may produce more male offspring and masculinized female offspring, leading to population decline. Unfortunately, the effects of prenatal hormone exposure have not yet been tested in lemmings. (Data from Shelford 1943.)

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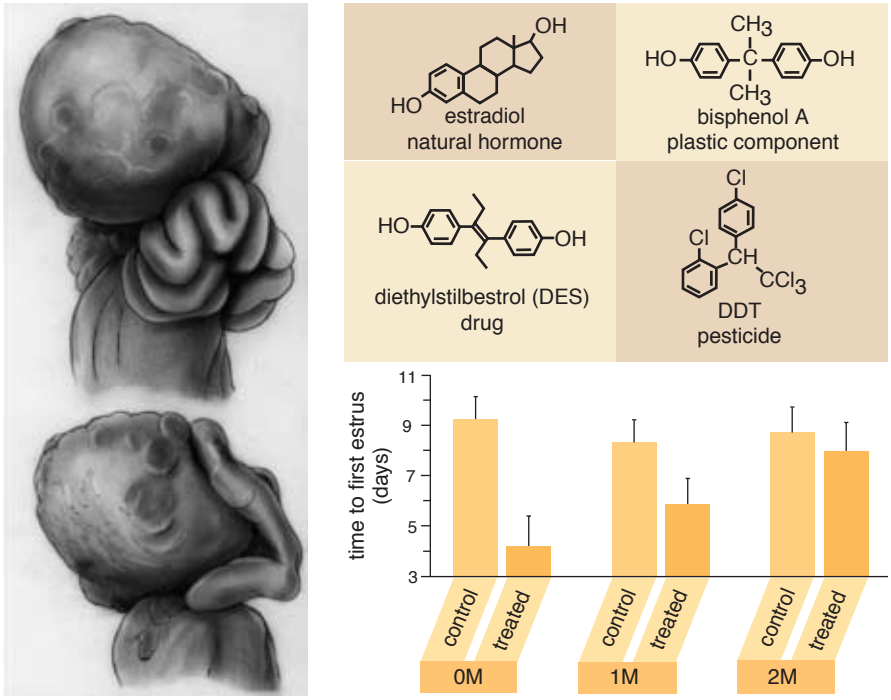

Figure 9. Prenatal treatment with the synthetic estrogen DES creates a variety of abnormalities in male and female mice. In normal females, the oviduct is tightly coiled between the ovary and uterus *(top left)*. In DES-treated females, this coiling does not proceed normally, and the oviduct becomes wrapped around the ovary *(bottom left)*. Compounds with estrogenic activity are difficult to identify based solely on chemical structure *(diagrams)*. Like the hormone estradiol, many estrogen mimics, including DES, bisphenol A and DDT, contain benzene rings, but other compounds with benzene rings show no endocrine-disrupting activity. Prenatal treatment with bisphenol A decreases the time to puberty in female mice, but the magnitude of the effect is correlated with intrauterine position *(bottom right)*. (Image from Newbold *et al.* 1983. Data from Howdeshell *et al.* 1999.)

As if that task wasn't daunting enough, there is the question of what concentrations of each chemical are likely to be in the environment, and what level of exposure should be tested for effects in the laboratory. A reasonable rule of thumb might be to test intermediate levels of exposure, but this approach may miss important effects at high or low doses. Surprisingly, endocrine disruptors may have opposite effects at low and high doses, or may have larger effects at low doses than at high or intermediate doses. These complications make testing 87,000 chemicals for endocrine disrupting activity an even more controversial and difficult prospect.

Because external endocrine disruptors interact with naturally variable hormone levels in the womb, these experiments must be carefully designed and analyzed. When testing for endocrine disrupting activity, researchers try to minimize variation in prenatal hormone exposure due to factors other than the chemical being tested. One such factor is intrauterine position. By comparing only animals from the same intrauterine position, researchers might be able to detect endocrine disrupting activity more reliably using fewer laboratory animals. Thus our understanding of intrauterine position suggests that endocrine disruptors may have important effects on development, and this understanding also has the potential to aid in the experimental design of studies that test the effects of potential endocrine disruptors.

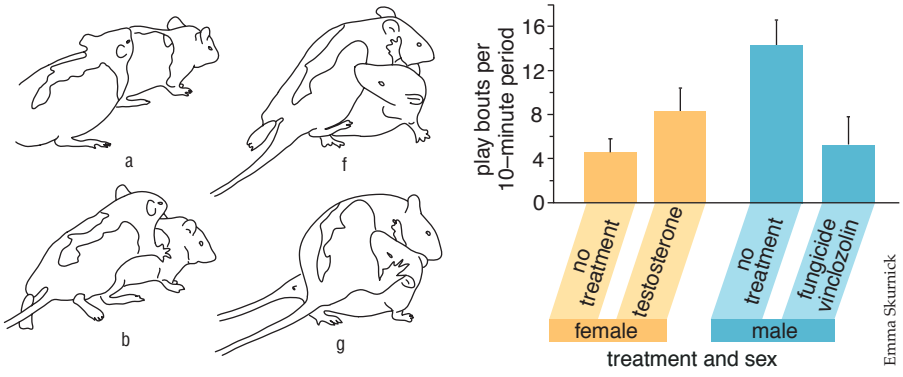

Figure 10. Juvenile male rats show more rough-and-tumble play than females. These drawings were selected from a description of play behavior by Pellis and Pellis (1987). Prenatal treatment with vinclozolin, an anti-androgen found in fungicides, reduces play in males. Conversely, prenatal treatment with testosterone increases play in females. (Data from Hotchkiss *et al.*, in press.)

Broader Applications

Hormonal effects on prenatal development are not confined to small mammals. Pigs also produce large litters that are lined up in the uterus, and the higher reproductive potential of 0M females might help breeders increase reproductive success in the pork industry. Even in animals that produce smaller litters, hormone exposure during development is important. Female sheep that had two male littermates as embryos are more likely to miscarry when they grow up and become pregnant themselves.

Human beings are not immune to the effects of prenatal hormone exposure. A study of 422 sets of British fraternal twins found that women with twin brothers are more likely to be uninhibited and adventurous than women with twin sisters. Of course these differences could be attributed to growing up in a household with a male playmate of the same age, but some other, non-behavioral differences in tooth and ear development also support the idea that sharing the womb with a member of the opposite sex impacts development in human beings. Although fraternal boy-girl twins are relatively rare, the recent increase in multiple births due to fertility treatment presents an interesting opportunity to study the impact of intrauterine hormone exposure in people.

Exposure to endocrine disruptors and other factors that influence hormone levels during pregnancy is likely to be much more widespread. Endocrine disruptors from plastics, pesticides, and household products easily make their way into our food and water, and may affect our reproductive bi-

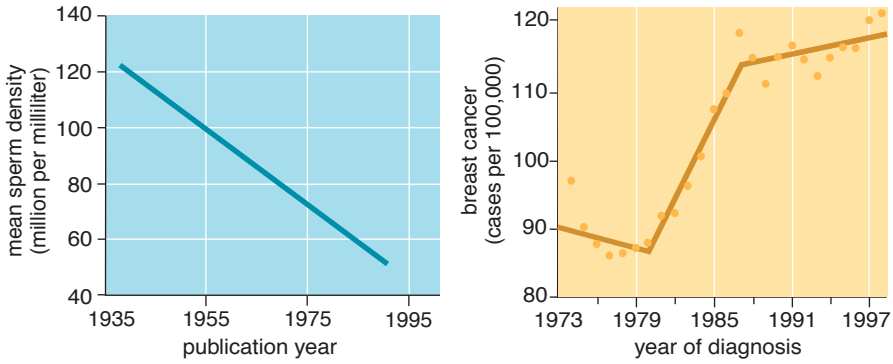

Figure 11. Long-term decreases in sperm count and increases in breast cancer in people have been blamed on endocrine disruptors in the environment. Some environmental chemicals have been shown to have endocrine disrupting activity in people, but it is difficult to pinpoint the causes of such long-term trends. Data shown are for U.S. men and U.S. white women. (Data from Swan *et al.* 1997 and Howe *et al.* 2001.)

ology and development. For example, exposure to a chemical derivative of the pesticide DDT has been linked to a shorter duration of breast-feeding in women in the United States and Mexico. Studies of women who ate PCB-contaminated fish from Lake Michigan during pregnancy have found that their children had reduced IQs and slowed intellectual development.

Prescription and non-prescription medications are another potential source of endocrine disruptor exposure. Treatment of pregnant women with the synthetic estrogen diethylstilbestrol *(Figure 9)* in the 1950s and '60s to prevent miscarriage caused abnormalities in reproductive anatomy in their children and increased susceptibility to a rare form of vaginal cancer in their daughters.

It has been suggested that several long-term trends in human health, including a reduction in sperm counts, earlier onset of puberty in girls and higher rates of breast and testicular cancer may be the result of exposure to environmental estrogens. Stress and malnutrition experienced by mothers during pregnancy can also alter endogenous hormone concentrations. The adult children of mothers who experienced these stressful conditions during pregnancy show greater susceptibility to a wide array of health problems, including diabetes, obesity, high blood pressure and heart disease.

One of the most rigorous recent demonstrations of the effects of prenatal hormone levels in human beings comes from an ongoing long-term study by Sheri Berenbaum of girls with congenital adrenal hyperplasia (CAH). Without treatment, CAH results in high levels of adrenal androgens during gestation and throughout life. Girls with CAH show increased male-like behaviors. They are more likely than their sisters to play with boy's toys and to show aggressive behavior, and less likely to show interest in infants. Once treated, many girls with CAH show a reduction in male hormone levels, but retain male-like behaviors. Berenbaum, now at Penn State University, and her colleagues have shown that these behavioral effects result from prenatal hormone exposure and not from postnatal, pre-treatment exposure.

Thus, human health, physiology and behavior may all be influenced by hormone levels during gestation. The full extent and nature of these effects in human beings and other animals have yet to be fully revealed, but what seems clear is that environmental effects contribute substantially to variation in sexual traits between individuals. Exposure to gonadal hormones and endocrine disruptors during fetal development is one of many ways that the environment interacts with our genetic makeup to make us who we are.

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