that showed up again and again in the tissue analyses of animals having trouble producing viable young. She quickly learned that the testing and reviews done by manufacturers and government regulatory agencies had focused largely on whether a chemical might cause cancer, but she found enough in the peer-reviewed scientific literature to prove that her hunch had been correct.

The hand-me-down poisons found in the fat of the wildlife had one thing in common: one way or another, they all acted on the endocrine system, which regulates the body's vital internal processes and guides critical phases of prenatal development. The hand-me-down poisons disrupted hormones.

Our Stolen Future

Colborn, Dumanoski, + Myers

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CHEMICAL MESSENGERS

PUSHING ON WITH HER RESEARCH ON HORMONES, THEO COLBORN DISCOVERED a central piece of the puzzle in the world of Frederick vom Saal, a biologist at the University of Missouri. Vom Saal's exploration of how hormones help make us who we are is a fascinating scientific adventure in its own right. In a series of experiments with mice, he showed that small shifts in hormones before birth can matter a great deal and have consequences that last a lifetime. His work helped highlight the hazard posed by synthetic chemicals that can disrupt hormonal systems.

Vom Saal's investigation of the wondrous world of hormones began in 1976 during his postdoctoral days at the University of Texas in Austin, inspired by the behavior of the lab mice. Like most postdoctoral biology students, vom Saal was spending the better part of his life in the lab, where his regular chores included breeding mice. As he played mouse matchmaker, arranging encounters between eager males and receptive females, he became intrigued by the interplay between the animals as he moved them from cage to cage.

In the beginning, the small, white, pink-eyed creatures had all

seemed like cookie-cutter copies of each other. But as he watched the females scurrying about in the breeding cages, individuals quickly emerged from the crowd. Whenever he returned a female to a group cage holding half a dozen females, there always seemed to be one mouse who would attack the intruder. These were mice with an attitude—tough cookies who rattled their tails threateningly and lashed out at their mild-mannered companions.

Such a difference between the behavior of one female and another was striking—and puzzling. The mice were all from a single laboratory strain that had been inbred for generations. When it came to genes, they were virtually identical.

This simple observation set the course for vom Saal's life's work in reproductive biology. In the years that followed, he designed dozens of experiments to probe the mystery of how two mice with almost the same genetic blueprint could behave so differently.

The notion persists that genes are tantamount to destiny and that one might explain everything from cancer to homosexuality by locating the responsible genes. But in a series of scientific papers, vom Saal demonstrated that there are other powerful forces shaping individuals—females as well as males—before birth. Genes, it turned out, are not the whole story. Not by a long shot.

What vom Saal saw during those long hours observing mice in the lab contradicted *everything* he had read. According to the scientific literature of the period (which reflected prevailing human assumptions as much as it described animal behavior), aggression was strictly a male behavior. But if tail-rattling, chasing, and biting among the females weren't aggression, what *would* one call it?

Eventually, vom Saal's colleagues had to concede that the behavior did look like aggression, but they tended to shrug it off as unimportant. Males were the center of the action in animal societies according to the prevailing wisdom in the field of animal behavior, so what females did simply didn't matter. They were just passive baby makers.

Vom Saal wasn't so sure. His intuition told him what he was seeing was probably important as well as interesting. His doctoral work had centered on the role played by testosterone in development

before birth, and he knew that this hormone—found at much higher levels in males—drives aggression.

From his observations, the tough females weren't common, but they weren't rare either. There seemed to be roughly one aggressive female for every six mice in the colony—something he noticed because the mice were housed six to a cage. If the mice were clones, something besides genes had to be shaping the aggressive females. Since birth the sisters had been raised identically, so living conditions could not explain the differences. Could the cause be something in their prenatal environment?

That set him to thinking about how mice are carried before birth. Their mother's womb isn't a single compartment like the human womb, but two separate compartments or "horns" that branch off to the left and the right at the top of the vagina or birth canal. The baby mice are tucked in the narrow horns like peas in a pod—as many as six on a side. This arrangement means that some of the females will develop sandwiched between two males.

Vom Saal began calculating probabilities. If there were twelve mice in the typical mouse litter and if the placement of males and females in the womb was random, how many females would end up between two males? Roughly one in six, he figured. That supported the theory taking shape in his head. Some of the females are markedly more aggressive, he suspected, because they had spent their prenatal life wedged between two males. A week before birth, the testicles in a male pup begin to secrete the male hormone testosterone, which drives his own sexual development. The female pups might be bathed in testosterone washing over from their male neighbors.

Maybe, vom Saal thought, the answer to the mystery of how genetically identical females could be so different lay in hormones—chemical messengers that travel in the bloodstream, carrying messages from one part of the body to another.

In the body's constant conversation with itself, nerves are just one avenue of communication—the one employed for quick, discrete messages that direct a hand to move away from a hot stove. A large part of the body's internal conversation, however, is carried on through the bloodstream, where hormones and other chemical messengers move about on the biological equivalent of the information

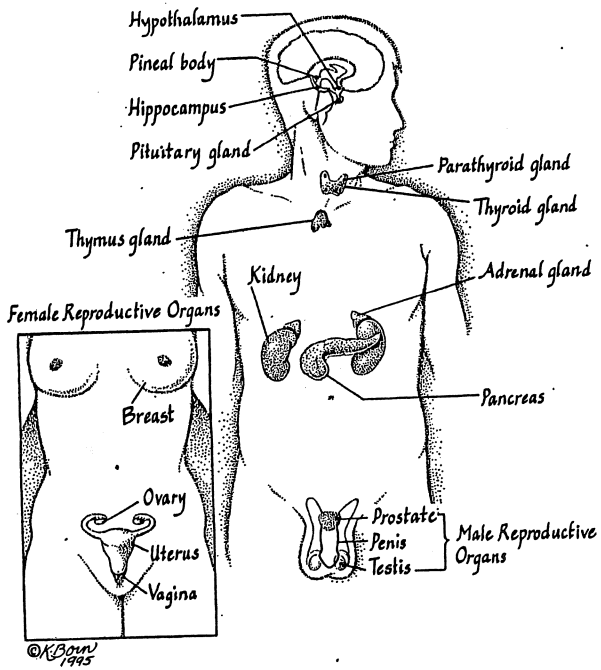
superhighway, carrying signals that not only govern sex and reproduction but also coordinate organs and tissues that work in concert to keep the body functioning properly.

Hormones, which get their name from the Greek word meaning "to urge on," are produced and released into the bloodstream by a variety of organs known as endocrine glands, including the testicles, the ovaries, the pancreas, the adrenal glands, the thyroid, the parathyroid, and the thymus. The thyroid, for example, produces chemical messengers that activate the body's overall metabolism, stimulating tissues to produce more heat. In addition to eggs, a woman's ovaries release estrogens—the female hormones that travel in the bloodstream to the uterus, where they trigger growth of the tissue lining the womb in anticipation of a possible pregnancy.

Yet another endocrine gland, the pituitary, which dangles on a stalk from the underside of the brain just behind the nose, acts as a control center, telling the ovaries or the thyroid when to send their chemical messages and how much to send. The pituitary gets its cues from a nearby portion of the brain called the hypothalamus, a teaspoon-size center on the bottom of the brain that constantly monitors the hormone levels in the blood in much the way that a thermostat monitors the air temperature in a house. If levels of a hormone get too high or too low, the hypothalamus sends a message to the pituitary, which signals the gland that produces this hormone to gear up, slow down, or shut off.

The messages travel back and forth continuously. Without this cross talk and constant feedback, the human body would be an unruly mob of some 50 trillion cells rather than an integrated organism operating from a single script.

As scientists have delved deeper into the nervous, immune, and endocrine systems—the body's three great integrating networks—they have encountered profound interconnections: between the brain and the immune system, the immune system and the endocrine system, and the endocrine system and the brain. The links sometimes seem utterly mystifying. How, for example, could a woman suffering from multiple personality disorder play with a cat for hours while she was one personality and suffer violent allergic reactions to cats when she took on another?



Some important glands, organs, and tissues sending or receiving hormonal messages in the human body.

Nobody knows the answer to this question, but it certainly lies in this internal conversation and the constant babble of chemical messengers. Changes in one part of this complex, interconnected system can have dramatic and unexpected consequences elsewhere, often where one might least expect, because everything is linked to everything else. A brain tumor, for example, might show up as disrupted menstrual cycles and hypersensitivity of the skin rather than as headaches.

If hormones are vital to maintain proper functioning in adults, they are perhaps even more important in the elaborate process of development before birth.

But how could vom Saal test his theory?

Mouse Caesarean sections.

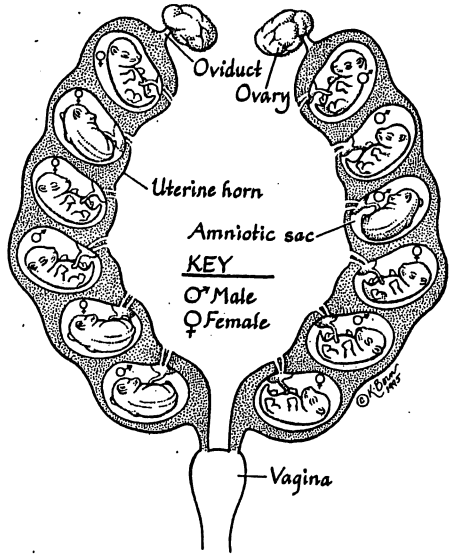
Just before the females were ready to give birth at the end of their nineteen-day pregnancies, vom Saal removed the tiny babies, who were approximately an inch long and about the size of an olive. He marked them based on their position relative to their neighbors in the womb. In this way, he could discover where aggressive females had spent their prenatal lives. Thus began vom Saal's exploration of what some in the field playfully refer to as the "wombmate" effect, known formally as intrauterine position phenomenon.

Although vom Saal is now forty-nine and a professor at the University of Missouri, he still looks youthful enough to be mistaken for a graduate student. In a scientific world where many seldom venture beyond narrow specialities, vom Saal embraces the big picture, unabashedly declaring that he is interested in "womb-to-tomb biology." He moves easily between elegant, tightly focused studies and a larger, more encompassing pursuit of fundamental questions: Why does this happen? What is the evolutionary significance?

Those first studies in Austin confirmed his theory. As the mice removed by Caesarean section matured, the aggressive females were, as predicted, the ones who had developed between brothers. Each intriguing finding raised new questions, leading to more studies and, in time, observations on thousands of mice delivered by Caesarean section. Aggression proved just the most obvious sign of profound differences between mouse sisters that could be predicted to a remarkable degree by their position in the womb.

At first blush, vom Saal's results sound like a tale of the ugly sister and the pretty sister. Not only was the ugly sister—the mouse that had developed between males—more aggressive, but vom Saal discovered she was significantly *less* attractive to males than the pretty sisters who had spent their womb time between other females. Eight times out of ten, a male given a choice would chose to mate with the pretty sister.

What's attractive to males isn't the female's tiny pink eyes or the curve of her tail. The social life of mice is governed by the nose, and the attractiveness of females depends on the social chemicals they give off, which are called pheromones. The pretty sisters smell "sexier" to males because they produce different chemicals than their less attractive sisters. The prenatal hormone environment leaves a



Behavioral and reproductive differences in mice can be predicted to a remarkable degree by their position, which is related to hormone exposure, in the womb. (Adapted from vom Saal and Dhar, 1992)

permanent imprint on each sister that is recognized by males for the rest of her life.

The sisters also showed dramatic differences in their reproductive cycles. Besides finding mates more readily, the pretty sister also matured faster than her ugly sister and came into heat—a period of sexual receptivity—more often. As a consequence, she had more opportunities to get pregnant and was more likely overall to produce more offspring in her lifetime than her aggressive, unattractive sister, who experienced puberty later and came into heat less frequently.

Even more amazing, studies by other researchers, including Mertice Clark, Peter Karpiuk and Bennett Galef of McMaster University, and the team of John Vandenbergh and Cynthia Huggett of North Carolina State University, have found that the wombmate effect even influences whether a female will give birth to more males or more females when she has pups of her own. This is mysterious indeed, since scientists up to now believed that the mother has no role

in determining the sex of her offspring. Based on current understanding, it is the sperm contributed by the father that dictates whether the egg develops into a male or female, so how a mother influences sex ratio is still unknown. However it happens, the pretty sisters tend to have litters made up of sixty percent females, while the ugly sisters generally give birth to litters that are roughly sixty percent male. As Vandenbergh wrote of this transgenerational wombmate influence: "Brothers beget nephews."

After hearing the tale of the two sisters, one might easily conclude that it would be wise to be a pretty sister if one had to be a mouse. They have lots of mates and babies and, judged by the evolutionary imperative of producing offspring, seem more successful than their ugly sisters.

Not so fast, vom Saal cautions. When one considers how these sisters live their lives within a mouse population that goes through boom and bust cycles, the pretty sister begins to lose her obvious edge. Typically, a mouse population builds to a very high peak and then it crashes. In ordinary times when the population isn't too dense, the pretty sisters definitely have the advantage, but as conditions become overcrowded the pretty sisters' ability to produce babies diminishes because the females respond to scent cues in urine that inhibit reproduction.

But these overcrowded times are precisely when the ugly sisters come into their own. Because they are relatively immune to the inhibiting cues, they are likely to be the only ones to produce offspring, and the ugly sisters are the only ones tough enough to protect their babies from attack and infanticide.

Interestingly, some studies have shown that the mother's physical condition can also alter hormone levels in the womb and influence the offspring. Mouse mothers that experience continuous stress through the latter part of their pregnancies give birth to females who have all the physical and behavioral characteristics of females who develop between males. Maternal stress seems to override the ordinary wombmate variations and produce a litter composed solely of tough cookies.

So what's the evolutionary lesson in this tale?

In vom Saal's view, the real lesson is the value of variability.

The acute sensitivity of developing mammals such as mice to slight shifts in hormone levels in the womb has been shaped by evolution. This characteristic helped insure wide variation in the offspring, even wider variation than that produced by genetic shuffling alone. Variation is the way mammals have hedged their bets in the face of a rapidly shifting environment. If you don't know what the conditions will be for your offspring, the best thing to do is produce many different kinds in the hope that at least one of them will be suited to the emerging moment.

Vom Saal's early investigations into the wombmate effect focused solely on females. The decision to look at males to see if female wombmates had any influence on them was almost an afterthought. Though the results would round out this line of research, vom Saal admits he frankly did not expect to find anything remarkable. It was widely assumed that male development was driven exclusively by testosterone, so being next to females should make little difference.

In fact, the results of his experiments astonished him. The wombmate effect shaped the destinies of males as well as females and in ways that no one would have *ever* predicted. In a major paper in the prestigious journal *Science* in June 1980, vom Saal and his associates laid out the case that it was exposure to the female hormone estrogen before birth that *increased* a male's sexual activity in adult life.

Inside and outside the world of science, many have regarded the level of male sexual activity as an index of masculinity and a product of the male hormone testosterone. Indeed, the findings were so counterintuitive and so contrary to assumptions about the "male" hormone testosterone and the "female" hormone estrogen that one of his collaborators protested that they must have somehow mixed up the samples. Vom Saal found, however, that estrogen and testosterone each influence males—and in ways that run counter to our conventional notions of "maleness" and "femaleness." The effect of wombmates on males proved an even more provocative vein of research than his earlier work on females.

If the females seem a story of the pretty and ugly sisters, then vom Saal's findings on the males sound like a tale of the playboy and the good father.

As adults, the playboy males, exposed to higher levels of estrogen

by their female wombmates, showed another surprising characteristic besides their higher rates of sexual activity. It would seem logical to assume that exposure to estrogen might make males more solicitous toward the young, but in fact, the opposite proved true. When placed with young mice, these males were more likely to attack and kill babies. The high-testosterone males who had had brothers for wombmates turned out to be the good daddies, who surprisingly showed almost as great an inclination to take care of pups as mouse mothers.

The playboy males were standouts in one other respect as well—the size of their prostate, the small gland that wraps around the urethra, through which urine is eliminated. The males exposed to higher levels of estrogen had prostates that were fifty percent larger than those seen in brothers who had had male wombmates. In addition, these larger prostates are more sensitive to male hormones in adulthood because they contain three times the number of testosterone receptors found in the prostates of brothers with male wombmates. More receptors generally means that the gland will grow more quickly in response to male hormones circulating in the bloodstream in adulthood.

Although human babies don't usually have to share the womb with siblings, their development can nevertheless be affected by varying hormone levels, which occur in the womb for reasons scientists don't completely understand. Medical problems such as high blood pressure can drive up estrogen levels, for example. Or perhaps eating tofu, alfalfa sprouts, or other foods that are high in plant estrogens during pregnancy could boost estrogen exposure. There is also the possibility that the mother's body fat contains synthetic chemicals that disrupt hormones.

Whatever the source, a recent study on opposite-sex human twins showed that wombmate effects can be detected in people as well. The study, which focused on an obscure difference in the auditory systems of males and females that exists from birth, found that girls who had developed with a boy twin showed a male pattern, suggesting that they, like vom Saal's female mice, had been somewhat masculinized by the hormones spilling over from a male wombmate.

In the midst of all these surprises, the male wombmate studies in mice yielded only one expected result—on male aggression. Males

with male wombmates and the highest testosterone exposure before birth were indeed the most aggressive toward other adult males, and males with female wombmates were the least aggressive.

Scientists working in this field are still debating how estrogen shapes the development of males and females, particularly the development of the brain and behavior, but vom Saal believes that estrogen is helping to masculinize males by acting to enhance some effects of the male hormone testosterone. Together the two hormones influence the organization of the developing brain to increase the level of sexual activity the male mouse will exhibit as an adult. Vom Saal had demonstrated that this is a prenatal effect rather than a consequence of adult hormone levels by castrating the mice shortly after birth and then in adulthood administering an identical amount of male hormone to brothers with male and female wombmates. Even with identical hormone exposure these male mice showed different levels of sexual activity—evidence that adult hormone levels are not the cause of these behavioral differences.

Those who hear about vom Saal's work typically ask him, Which is the "normal" mouse: the pretty sister or the ugly sister? The playboy or the good father?

"They're *all* normal," vom Saal says emphatically.

The question itself seems to stem from our dualistic notion of maleness and femaleness, which sees the two sexes as mutually exclusive categories. In fact, there are many shades of gray and overlap between behaviors thought of as typically male or female. Seen in this light, there is nothing abnormal about an aggressive female or a nurturing male. In this strain of mice, whose genetic variability has been reduced by generations of inbreeding, these individuals reflect the variability created by the natural influence of hormones before birth. What is "normal," vom Saal says, returning to an evolutionary theme, is not one type of individual or another but the variability itself.

But variability is just one of the larger lessons emerging from vom Saal's work. It has also opened a window on the powerful role of hormones in the development of *both* sexes and the extreme sensitivity of developing mammals to slight shifts in hormone levels in the womb. The wombmate studies have also underscored that hormones *permanently* "organize" or program cells, organs, the brain, and

behavior *before birth*, in many ways setting the individual's course for an entire lifetime.

It is important to remember that hormones do this without altering genes or causing mutations. They control the "expression" of genes in the genetic blueprint an individual inherits from its parents. This relationship is similar to that between the keys on a player piano and the prepunched music roll that runs through and determines the tune. Though the piano can theoretically play many tunes, it will only play the one dictated by the pattern of holes in the music roll. During development, hormones present in the womb determine which genes will be expressed, or played, for a lifetime as well as the frequency of their expression. Nothing has been changed in the individual's genes, but if a particular note hasn't been punched into the music roll during development, it will remain forever mute. Genes may be the keyboard, but hormones present during development compose the tune.

What is astonishing about vom Saal's wombmate studies is how *little* it takes to dramatically change the tune. Hormones are exceptionally potent chemicals that operate at concentrations so low that they can be measured only by the most sensitive analytical methods. When considering hormones such as estradiol, the most potent estrogen, forget parts per million or parts per billion. The concentrations are typically parts per trillion, one thousand times *lower* than parts per billion. One can begin to imagine a quantity so infinitesimally small by thinking of a drop of gin in a train of tank cars full of tonic. One drop in 660 tank cars would be one part in a trillion; such a train would be six miles long.

The striking lifelong differences between a pretty sister and ugly sister stem from no more than a thirty-five parts per trillion difference in their exposure to estradiol and a one part per billion difference in testosterone. Using the gin and tonic analogy, the pretty sister's cocktail had 135 drops of gin in one thousand tank cars of tonic and the ugly sister's 100 drops—a difference that might not be detectable in a glass much less in a tank car flotilla.

This is a degree of sensitivity that approaches the unfathomable, a sensitivity, vom Saal says, "beyond people's wildest imagination." If such exquisite sensitivity provides rich opportunities for

varied offspring from the same genetic stock, this same characteristic also makes the system vulnerable to serious disruption if something interferes with normal hormone levels—a frightening possibility that first dawned on vom Saal when Theo Colborn called him to talk about synthetic chemicals that could act like hormones.

To appreciate vom Saal's concern, one must understand more about the intricate choreography of events before birth known as sexual differentiation and the key role played by hormones in this developmental ballet. In mice, elephants, whales, humans, and all other mammals as well as in birds, reptiles, amphibians, and fish, the process that creates two sexes from initially unisex embryos is guided by these chemical messengers. They are the conductors that give the cues at the right moment as tissues and organs make now-or-never choices about the direction of development. In this central drama in which boys become boys and girls become girls, hormones have the starring role.

Our understanding of what determines whether a fertilized egg becomes a male or female is very recent. Before the twentieth century, it was widely assumed that the sex of the baby was determined by environmental factors such as temperature.

It was only in 1906 that two scientists—Nettie Marie Stevens and Edmund Beecher Wilson—independently noted that each cell in women had two X chromosomes while men always had an X and a Y, an observation that led to the theory that the number of X chromosomes determined sex. In the past decade, researchers have finally established that it is a gene on the Y chromosome rather than the number of X chromosomes that determines sex.

As most of us learned in high school biology, the eggs produced by the mother all carry one X chromosome, and the sperm from the father carry either an X or a Y chromosome. The sex of the baby hangs in the balance as the sperm burst out of the starting gate and race against each other in the reproductive marathon. If this most primordial of athletic events were broadcast like the Boston Marathon, we might hear that three Ys are neck-and-neck at the entrance to the cervix, but an X is making a move on the outside in the push into the uterus. A field of 75 million sperm have been pushing hard, sweeping their tails back and forth in steady swimming motions, but in the

biological equivalent of Heartbreak Hill, many are beginning to flag as they enter the fallopian tube leading from the top of the uterus. It's a tight race right to the finish line as the competitors crowd toward the goal. At the finish line of this race, an egg awaits the victor, rather than a crown of laurel, as it crashes through. If the Y-carrying sperm gets to the egg first, the baby, who has XY chromosomes, will be a boy. If the first sperm to the egg carries an X, the XX chromosome will produce a girl.

Such stories about the race between the Xs and the Ys for the egg left many of us with the impression that the outcome was all in the genetic instructions carried by the sperm. If the sperm delivered a Y, bingo, it was a boy—what unfolded between conception and birth was all more or less automatic and dictated by that genetic blueprint. In fact, the process is much more complex. The sex-determining gene in that Y chromosome has only a quick walk-on part in the elegant and wondrous process through which boys become boys.

In animals such as birds and humans, one sex is the basic model and the other is what might be described as a custom job, since the latter requires a sequence of additional changes directed by hormones to develop properly into the opposite sex. In birds, this basic model happens to be male. In mammals, including humans, the opposite is the case, and an embryo will develop into a female unless male hormones override the program and set it off on the alternative course.

Although the sperm delivers the genetic trigger for a male when it penetrates the egg, the developing baby does not commit itself to one course or another for some time. Instead, it retains the potential to be either male or female for more than six weeks, developing a pair of unisex gonads that can become either testicles or ovaries and two separate sets of primitive plumbing—one the precursor to the male reproductive tract and the other the making of the fallopian tubes and uterus. These two duct systems, known as the Wolffian and Müllerian ducts, are the only part of the male and female reproductive systems that originate from different tissues. All the other essential equipment—which might seem dramatically different between the two sexes—develop from common tissue found in both boy and girl fetuses. Whether this tissue becomes the penis or the clitoris, the scrotal sack that carried the testicles or the folds of labial flesh around a woman's vagina, or something in between depends on the hormonal cues received during a baby's development.

The big moment for the Y chromosome comes around the seventh week of life, when a single gene on the chromosome directs the unisex sex glands to develop into male testicles. In doing this, the Y chromosome throws the switch initiating the very first step in male development, the development of the testes, and that is the beginning and end of its role in shaping a male. From this point on, the remainder of the process of masculinization is driven by hormone signals originating from the baby's brand-new testicles. In adult life, the testicles produce sperm to fertilize a woman's eggs, the male's contribution to reproduction and posterity. But the testicles play an even more important role in a male's life before birth. Without the right hormone cues at the right time—cues emanating from the testicles—the baby will not develop the male body and brain that go along with the testicles. It might not even develop the penis required to deliver the sperm the testicles produce.

In girls, the changes that turn the unisex glands into ovaries, the part of the female anatomy that produces eggs, begin somewhat later, in the third to fourth month of fetal life. During this same period, one set of ducts—the Wolffian ducts that provide the option for a male reproductive tract—wither and disappear without any special hormone instructions. While the development of the female body isn't as dependent on hormone cues as the development of males, animal research suggests estrogen is essential for proper development and normal functioning of the ovaries.

The process of laying the groundwork for the reproductive tract is more complicated in males and is marked by critical stages where hormones direct now-or-never decisions. Shortly after they are formed, the testicles produce a special hormone whose function is to trigger the disappearance of the female option—the Müllerian ducts. To accomplish this milestone, the hormone message must arrive at the right time, because there is only a short period when the female ducts respond to the signal to disappear. Then the testicles have to send another message to the Wolffian ducts, because they are programmed to disappear automatically by the fourteenth week unless they receive orders to the contrary.

The messenger is the predominantly male hormone testosterone, which insures the preservation and growth of the male Wolffian ducts. Under the influence of testosterone, these ducts form the epididymis, vas deferens, and seminal vesicles—the sperm delivery system that leads from the testicles to the penis.

A potent form of testosterone guides the development of the prostate gland and external genitals, directing the genital skin to form a penis and a scrotum that holds the testicles when they finally descend from the abdomen late in a baby's development. A naturally occurring defect dramatically illustrates what can happen if these messages do not get through.

From time to time, a young patient will show up in a gynecologist's office because the teenager still hasn't had her first period although all the other girls in her class have passed this milestone. Usually nothing serious is wrong.

But once in a rare while, the physician will deliver an utterly shocking diagnosis. The patient isn't menstruating because despite all appearances, she is *not* female. Although such individuals have grown up as normal-looking girls, they have the XY chromosomes of males and testicles in their abdomen instead of ovaries. But because a defect makes them insensitive to testosterone, they never responded to the hormone cues that trigger masculinization. They never developed the body and brain of a male.

The pictures in medical textbooks of these unrealized males are fascinating, for there is nothing about their unclothed bodies that looks the least bit odd or unusual. As hard as one searches for a hint that a genetic male lurks inside these bodies, there is no sign of development derailed. These genetic males look like perfectly ordinary women with normally developed breasts, narrow shoulders, and broader hips.

These completely feminized males are the most extreme example of what happens when something blocks the chemical messages that guide development. If anything interferes with the testosterone or the enzyme that amplifies its effect, the common tissue found in boy and girl fetuses will develop instead into a clitoris and other external female genitals. In less extreme cases of disruption, males may have ambiguous genitals or abnormally small penises and undescended testicles.

But sex is more than a purely physical matter. According to physicians who treat them, these feminized males not only look like women, they act and think of themselves as women. There is nothing the least bit telling in their behavior to suggest that they are really male. In most animals, the development of a properly functioning male or female involves the brain as much as the genitals, and research such as vom Saal's shows that hormones permanently shape some aspects of behavior before birth as much as they sculpt the penis. If an individual is going to act like a male as well as look like one, the brain must receive testosterone messages from the testicles during a critical period when brain cells are making some of their now-or-never decisions.

An individual who gets the wrong hormone messages during this critical period of brain development may show abnormal behavior and fail to mate even though it has the right physical equipment. In an influential 1959 study, Charles Phoenix of the University of Kansas found that female guinea pigs exposed to high levels of testosterone in the womb acted like males. They would not show the classic female mating posture, a raised posterior, known as "lordosis," as adults or respond normally to the female hormones that stimulate sexual behavior and reproduction.

No one debates that hormones act to give males and females different bodies and that their role in the development of animals and humans is pretty much the same. But how hormones influence the development of the human brain is hotly debated. Do they shape the brain and behavior in humans as dramatically as they do in mice or rats or guinea pigs? Are there structural differences between the brains of men and women, and is there any evidence that the differences stem from hormone influences before birth?

These questions are difficult to answer. Not only is human behavior more complex than that of vom Saal's mice, but we aren't free to give pregnant women various doses of hormones to see the effect on the brain development of their babies.

Those who have probed the question of whether the behavioral differences between men and women have a biological basis or are purely cultural have found evidence of some structural differences linked to hormones, but so far these sex-linked areas are fewer and

less pronounced than those seen in rats. Psychologists have also reported certain general differences in the way men and women think, reporting that women have greater verbal skills as a rule and men tend to be better at solving spatial problems. Many also believe that the rough-and-tumble play and fighting seen to a much greater degree in young boys than in girls stems from biology rather than from culture or child-rearing methods.

At the same time that hormones are guiding at least some aspects of sexual development of the unborn child, these chemical messengers are also orchestrating the growth of the baby's nervous and immune systems, and programming organs and tissues such as the liver, blood, kidneys, and muscles, which function differently in men and women. Normal brain development, for example, depends on thyroid hormones that cue and guide the development of nerves and their migration to the right area in this immensely complex organ.

For all these systems, normal development depends on getting the right hormone messages in the right amount to the right place at the right time. As this elaborate chemical ballet rushes forward at a dizzying pace, everything hinges on timing and proper cues. If something disrupts the cues during a critical period of development, it can have serious lifelong consequences for the offspring.

4

HORMONE HAVOC

AS WE PURSUE THE MYSTERY OF HAND-ME-DOWN POISONS, TWO TRAGIC episodes in medical history contain important lessons and immediate relevance to our quest. They leave no doubt that humans are vulnerable to hormone-disrupting synthetic chemicals and demonstrate that animal studies had repeatedly provided an early warning about the hazards for humans.

From the very beginning, these warnings were clear and ominous. As early as the 1930s, researchers at Northwestern University Medical School showed that tinkering with hormone levels during pregnancy was dangerous business, particularly for the fetus undergoing rapid development in the womb. In some of the experiments, the researchers simply gave an extra dose of estrogen to pregnant rats, who already have this female hormone in their bodies. The impact on their pups proved dramatic. At birth, the rat offspring showed striking abnormalities stemming from disrupted sexual development. The female pups exposed to extra natural or synthetic estrogen in the womb suffered structural defects of the uterus, vagina, and ovaries; males had stunted penises and other genital deformities.