In the Moment

Somewhere Between a Boy and a Girl

Darshak Sanghavi, MD

Ambulatory Pediatrics 2008;8:1–3

Some years ago, I was called for a consultation to see a young professional couple. I'll call them the Raskins. They were about to have a baby boy and wanted to know the arguments for and against circumcision. But that question would soon be dwarfed by another, larger question once we saw the baby's genitals.

I remembered assisting in a circumcision as an intern. An obstetrician and I had strapped the baby spread-eagled to a contraption to hold him. We first injected lidocaine at the penis's base. Although this seems obviously humane, only recently have most infants received pain control during circumcision, a practice stemming from a belief that babies can't localize, feel, or remember pain. However, they clearly cry, have increased blood pressure, and release copious amounts of stress hormones like cortisol into the bloodstream. In 1997, a team of Canadian researchers found that an anesthetic cream applied to the penis reduced stress in babies undergoing circumcision, a finding deemed so revolutionary that no less an authority than the *New England Journal of Medicine* featured the article prominently to educate the medical community that, yes, babies in fact can feel pain.

The boy slowly calmed down, and we prepared our instruments. The human penis begins development at 1 to 2 months' gestation, and the foreskin that covers the penile head starts forming a month later. Initially, the foreskin adheres to the penile head as avidly as the skin on an apple. Over time, in a process not complete in some boys until after 5 years of age, the foreskin gradually separates from the penis, forming a retractable sleeve. Because the foreskin hadn't yet separated completely, I used a blunt probe to peel it back from the penis, as if shucking an ear of corn. We cut the foreskin circumferentially around the base of a bell protecting the glans, until it came off in one segment like a section of calamari. The ancient procedure—which is depicted even on Egyptian tombs—took only 90 seconds.

Darshak Sanghavi, MD, is a health journalist and pediatric cardiologist at the University of Massachusetts Medical School.

From the Division of Pediatric Cardiology, University of Massachusetts Medical School, Worcester, Mass.

Address correspondence to Darshak Sanghavi, MD, Division of Pediatric Cardiology, Rm S5-715, University Campus, University of Massachusetts Medical School, 55 Lake Ave N, Worcester, Massachusetts 01655 (e-mail: sanghavi@post.harvard.edu).

To meet the Raskins, I walked to the labor and delivery wing. Jim and Emily Raskin, both lawyers in their early 30s, hadn't yet decided whether to circumcise their child, whose prenatal sonogram had suggested male sex. The literature around circumcision is highly confounded, and it's thus hard to be definitive about the practice. "Could you give the arguments for and against it?" asked Jim, a tallish man with owl-like spectacles.

I outlined the information for the Raskins, who listened quietly. "The bottom line," I hedged, "is that there is no consensus. It's your decision." Emily looked at James and nodded knowingly, then thanked me. Because Emily was having a planned cesarean section, I'd be present at the delivery to resuscitate the newborn if needed. "See you soon," I said, and left.

As Emily was being taken into the operating room, I changed into scrubs and shot the breeze with the circulating nurse. "Water's broken," I heard. From out of my field of view came newborn screams, and James cried, "He's here!"

The obstetrician looked up at James and, while removing the baby, called out, "Congratulations. You have a beautiful…" A pause ensued as the doctor saw the child's genitals. He concluded, "…child."

The scrub nurse handed the infant to me, and I brought the child over to the warmer and dried the writhing, slippery body with clean towels. The baby's color rapidly went from blue to a healthy rosy shade. But there was an immediate problem: I couldn't tell if the baby was a boy or girl.

At the baby's perineum, there was a 1-cm-long appendage that looked like a penis. At the base, though, in place of a scrotum containing testicles, there instead a lengthwise opening bordered by swollen tissue resembling labia majora. The child possessed parts of both sexes, and I couldn't assign a male or female gender. The child had ambiguous genitalia.

"Your child has a problem with the genitals," I said to James, after walking over. "It's unclear whether you had a boy or girl, and we'll need to do some tests to investigate." I wrapped the child in clean linens and handed the newborn over. James kissed the baby's forehead and looked worried. Still sedated, Emily slept. Her husband would have to break the news when she woke. I explained the evaluation to James and tried to offer some reassurance. Then he handed his baby back to me, and I took the child to the neonatal intensive care unit (NICU) to determine what happened to the gonads during their development.

We all have an inborn tendency to develop into females. That is, a developing human's gonads at 1 to 2 months'

gestation become ovaries when left alone. Internal pouches called Müllerian ducts gradually become the fallopian tubes, uterus, and upper vagina, and externally the labia minora and majora appear; this is the default pathway of our bodies.

It is the presence of a single piece of DNA called the *SRY* gene—the key portion of the Y chromosome—that turns males into males. Most pediatricians rarely marvel at the poetry of the endocrine system. By a process not fully understood, the *SRY* gene makes the month-old gonads inside the fetus's abdomen into testicles. But that isn't what ultimately makes one into a male. A remarkable cascade ensues that involves HCG, which percolates from the placenta into the fetal bloodstream and induces the testes to make testosterone. Thus, those of us who do become male do so only because our mothers' bodies decree it.

A child with ambiguous genitals almost always has 1 of 2 conditions. There could be female genes but a hidden source of male hormones. This child would have ovaries. Alternatively, there could be male genes but some problem in making or responding to male hormones. In this situation, the child would have testes (sometimes hidden in the abdomen).

In the NICU, James and Emily Raskin's baby was placed in an open bassinet. Usually the cribs of NICU entrants have blue or pink cards with the child's name. Our new patient got a white one. Because English has no gender-neutral pronoun for people (the word *it* seems inappropriate), we referred to our charge repeatedly as "the baby."

The attending neonatologist and I conferred. He recommended that we first determine what the baby's chromosomes were. We drew a whiff of blood and sent it to the lab immediately, but an answer would take 48 hours. Then he called a radiologist to delineate the baby's internal anatomy. Finally, we drew some more blood to measure various hormone levels. "For now," he said, "we wait." He walked away, tapping various bassinets in his path.

I looked down at our patient, who stirred briefly before turning to one side and falling asleep, perhaps dreaming.

The workings of infants' brains are enigmatic, especially regarding the development of sexual identity. In 1967, a family practitioner performed a negligent circumcision on a healthy newborn boy and destroyed the penis. The child was assessed by Dr John Money, a sexologist from Johns Hopkins, who advised the boy's parents to complete a sex change operation on the child, hide his birth sex from him, and raise him as a girl. Money subscribed to the notion that sexual identity is socially constructed and thus malleable. But as described by reporter John Colapinto in his book *As Nature Made Him*, the child grew up with great sexual frustration and ambivalence, and after growing up as a girl decided to live as an adult man.

In this regard, the transformation of *guevedoces,* a group of children from southwestern Dominican Republic, is instructive. Certain male fetuses are unable to produce a form of testosterone called DHT because they lack an enzyme in their developing genitals. Consequently, these newborns have testes and numerous male structures that remain in the abdomen, but have exterior genitals that appear female. They are initially reared as girls, because that is what they look like.

But around puberty, the pituitary gland activates the testes to make large amounts of testosterone. Although DHT is still absent, testosterone in these large quantities can mimic its effects. Suddenly, in early puberty, these individuals begin growing a penis. (*Guevedoces* literally means "penis at 12 years.") They develop a deepened voice, chest hair, and other signs of maleness. They subsequently live as males, identify themselves as males, and may report that they always felt like males trapped in female bodies. This further supports the lessons of the Hopkins case: a person's gender identity may be shaped very early in development by testosterone.

For the Raskins, the radiologist was the first to present helpful information. The sonogram showed that the child internally had a uterus and vagina. The Müllerian ducts had not withered, which meant that no anti-Müllerian hormone (AMH) was ever made. It was therefore likely that the child didn't have testicles (which would have made AMH), but ovaries. In addition, there did not appear to be any obvious male structures other than the small appendage resembling a penis.

It was likely that the child was a genetic female, meaning she had two X chromosomes. Why, then, did the baby have a partial penis? We found out very shortly, when the lab called with the results of a blood test.

The answer begins with a complex, commonly known molecule that is the building block of our sex hormones. Biochemist Joseph Goldstein calls it "the most highly decorated small molecule in biology," since 13 Nobel Prizes have been awarded for its study. Among other functions, various hormones derived from it shape our genitals, maintain our blood pressure, build up our muscles, and help fight infection. Primarily made by the liver, the molecule begins with tiny pieces of sugar that are joined, twisted, and oxidized in a dizzying series to make an end product faintly resembling the interlinked Olympic rings. This molecule is cholesterol.

Like crude oil, cholesterol is transported from the site of its production, the liver, by tankers called chylomicrons to refineries throughout the body. In the testes, for example, cholesterol brought by chylomicrons is converted into testosterone. In the ovaries, it is made into estrogen, and in the kidneys it becomes a form of vitamin D. The body tightly regulates the supply of refined products in the body's metabolic economy. For example, when the body has enough testosterone, the testes cut back on their production through a feedback loop. When the system gets disrupted, though, a hormone glut develops.

Something like this happened to the Raskins' baby. The child couldn't make cortisol as a result of congenital adrenal hyperplasia. So the adrenal gland just kept making the only cholesterol-based hormone it could make: an analogue of testosterone. Although female, the baby experienced a glut of male hormone that enlarged her clitoris so that it looked like a small penis.

An endocrine specialist explained the findings to the Raskins. The neonatologist and I spoke again at the baby's bedside, and we wrote orders to begin administration of cortisol hormones by mouth. This would satisfy the baby's need and reduce the signal for continued adrenal hormone production. The male hormones would go back to normal levels for a female.

I reached for a pink card and began to fill it out with the words "Raskin, Baby Girl." The endocrinologist recommended surgical remodeling of the genitals to a more female form. Her other blood test, when it returned, confirmed that she had two X chromosomes. In some way, this released some tension: the baby finally had a sexual identity.

But did she?

In 1975, Anke Ehrhardt compared 17 patients like Baby Girl Raskin to their healthy sisters to study their gender identity. All the patients had had surgery to appear female and took replacement hormones by mouth, just as we had recommended for our patient. The results of Ehrhardt's follow-up were fascinating. The young CAH patients preferred boys as playmates half the time, compared with less than 5% of the time for their healthy sisters. Although almost all the normal sisters played with dolls, fewer than 1 in 10 of the CAH patients did. The differences persisted well into adolescence; 60% of the CAH patients were "tomboyish" and had no interest in jewelry and makeup, compared with less than 10% of their siblings. A 1984 study found that 40% of adult women with CAH said they were "exclusively heterosexual" and that 35% were "bisexual or homosexual."

This information demonstrates the complexity of gender assignment. Although these girls and women with CAH had two X chromosomes, ovaries, externally female genitals, and adequate levels of female hormones, they continued to have characteristics societally viewed as male, perhaps due to their prenatal exposure to male hormones. How, then, should maleness and femaleness be defined? Psychologists today view gender as a collection of 5 independent qualities: genetic makeup, external appearance, brain organization, sexual orientation, and personal gender identity. Thus, a typical woman is female in all areas. A person with CAH, however, may have female genes, external appearance, and gender identity, but male brain organization and sexual orientation. A person with gender dysphoria—that is, someone who might seek a sex change operation—may be a particular sex in all matters except gender identity. And a gay man, for example, might be male in all aspects except sexual orientation.

In a sense, children like Baby Girl Raskin challenge our tendency to simplify very complex psychological and medical phenomena. Although it's likely that she will be metabolically healthy, her future will not be easy. To function in society, will she have to pigeonhole herself into a gender role that may confine her true nature? How might her peers treat a little girl who doesn't like dolls, or a tomboyish teenage girl with little interest in clothing or makeup? How will her parents react if she is a lesbian? Will she, by some measure, remain true to herself? And even if she does, how will the world respond to her?

In medical training, perhaps we fixate on metabolic pathways because they explain, quite beautifully, the delicate homeostatic webs that regulate living things. It is tempting to wax rhapsodically about them. In the end, though, this knowledge only provides the most evanescent sense of order: we may know everything about the production and regulation of steroid hormones, yet know nothing about the futures of children like Baby Girl Raskin. As physicians, we often assume that by knowing the origins of disease, we may offer useful treatments. But that's not always how it works. Instead, we're confused on a different level, offering life-saving treatment but not really understanding the life we have saved. It comes as no surprise that our patients sometimes must face the future with the same anticipation and dread that they always have—and we hope to ease their way slightly by offering up our tiny morsels of knowledge.