**Sex biology redefined: Genes don’t indicate binary sexes**

[Andrea Ford](http://scopeblog.stanford.edu/author/alillyf/) on February 24, 2015

<http://scopeblog.stanford.edu/2015/02/24/sex-biology-redefined-genes-dont-indicate-binary-sexes/>

Imagine being a forty-six-year-old woman pregnant with her third child, whose amniocentesis follow-up shows that half her cells carry male chromosomes. Or a seventy-year-old father of three who learns during a hernia repair that he has a uterus. A recent news [feature](http://www.nature.com/news/sex-redefined-1.16943#/spectrum) in *Nature* mentioned these cases as it elaborated on the *spectrum* of sex biology. People can be sexed in a non-straightforward way and not even be aware of it; in fact, most probably aren’t. As many as 1 person in 100 has some form of “DSD,” a difference/disorder of sex development.

The simple scenario many of us learned in school is that two X chromosomes make someone female, and an X and a Y chromosome make someone male. These are simplistic ways of thinking about what is scientifically very complex. Anatomy, hormones, cells, and chromosomes (not to mention personal identity convictions) are actually not usually aligned with one binary classification.

The *Nature* feature collects research that has changed the way biologists understand sex. New technologies in DNA sequencing and cell biology are revealing that chromosomal sex is a *process*, not an assignation.

As quoted in the article, [Eric Vilain](http://socgen.ucla.edu/people/eric-vilain/), MD, PhD, director of the [Center for Gender-Based Biology](http://gendercenter.genetics.ucla.edu/) at UCLA, explains that sex determination is a contest between two opposing networks of gene activity. Changes in the activity or amounts of molecules in the networks can sway the embryo towards or away from the sex seemingly spelled out by the chromosomes. “It has been, in a sense, a philosophical change in our way of looking at sex; that it’s a balance.”

What’s more, studies in mice are showing that the balance of sex manifestation can be shifted even after birth; in fact, it is something actively maintained during the mouse’s whole life.

According to the *Nature* feature, true intersex disorders, such as those from divergent genes or the inability of cellular receptors to respond to hormones, yield conflicting chromosomal and anatomical sex. But these are rare, about 1 in 4,500*.* For the 1/100 figure, they used a more inclusive definition of DSDs. More than 25 genes that affect sex development have now been identified, and they have a wide range of variations that affect people in subtle ways. Many differences aren’t even noticed until incidental medical encounters, such as in the opening scenarios (the first was probably caused by twin embryos fusing in the woman’s mother’s womb; the second by a hormonal disorder).

Furthermore, scientists now understand that everyone’s body is made up of a patchwork of genetically distinct cells, some of which may have a different sex than the rest. This “mosaicism” can have effects ranging from undetectable to extraordinary, such as “identical” twins of different sexes. An extremely common instance of mosaicism comes from cells passing over the placental barrier during pregnancy. Men often carry female cells from their mothers, and women carry male cells from their sons. Research has shown that these cells remain present for decades, but what effects they have on disease and behavior is an essentially unstudied question.

This is an uneasy way to think about bodies in a social world where sex is still defined in binary terms. Legal frameworks rely on being able to classify someone as male or female, and social status is often determined by the sex on a birth certificate. Parents and doctors of intersex infants face thorny ethical questions about potential surgeries, therapies, and how to raise the child. The implications of better understanding and socially recognizing DSDs are huge.

As our understanding of biology continues to advance, our social, legal, and medical systems will have to evolve as well. Check out the *Nature* [feature](http://www.nature.com/news/sex-redefined-1.16943#/spectrum) article below for a discussion of these problems, as well as more interesting research into the biology of sex.

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**Sex Redefined**

The idea of two sexes is simplistic. Biologists now think there is a wider spectrum than that.

[Claire Ainsworth](http://www.nature.com/news/sex-redefined-1.16943#auth-1)[1](http://www.nature.com/news/sex-redefined-1.16943#a1) 18 February 2015

<http://www.nature.com/news/sex-redefined-1.16943#/spectrum>

As a clinical geneticist, Paul James is accustomed to discussing some of the most delicate issues with his patients. But in early 2010, he found himself having a particularly awkward conversation about sex.

A 46-year-old pregnant woman had visited his clinic at the Royal Melbourne Hospital in Australia to hear the results of an amniocentesis test to screen her baby's chromosomes for abnormalities. The baby was fine — but follow-up tests had revealed something astonishing about the mother. Her body was built of cells from two individuals, probably from twin embryos that had merged in her own mother's womb. And there was more. One set of cells carried two X chromosomes, the complement that typically makes a person female; the other had an X and a Y. Halfway through her fifth decade and pregnant with her third child, the woman learned for the first time that a large part of her body was chromosomally male[1](http://www.nature.com/news/sex-redefined-1.16943#b1). “That's kind of science-fiction material for someone who just came in for an amniocentesis,” says James.

Sex can be much more complicated than it at first seems. According to the simple scenario, the presence or absence of a Y chromosome is what counts: with it, you are male, and without it, you are female. But doctors have long known that some people straddle the boundary — their sex chromosomes say one thing, but their gonads (ovaries or testes) or sexual anatomy say another. Parents of children with these kinds of conditions — known as intersex conditions, or differences or disorders of sex development (DSDs) — often face difficult decisions about whether to bring up their child as a boy or a girl. Some researchers now say that as many as 1 person in 100 has some form of DSD[2](http://www.nature.com/news/sex-redefined-1.16943#b2).

When genetics is taken into consideration, the boundary between the sexes becomes even blurrier. Scientists have identified many of the genes involved in the main forms of DSD, and have uncovered variations in these genes that have subtle effects on a person's anatomical or physiological sex. What's more, new technologies in DNA sequencing and cell biology are revealing that almost everyone is, to varying degrees, a patchwork of genetically distinct cells, some with a sex that might not match that of the rest of their body. Some studies even suggest that the sex of each cell drives its behaviour, through a complicated network of molecular interactions. “I think there's much greater diversity within male or female, and there is certainly an area of overlap where some people can't easily define themselves within the binary structure,” says John Achermann, who studies sex development and endocrinology at University College London's Institute of Child Health.

These discoveries do not sit well in a world in which sex is still defined in binary terms. Few legal systems allow for any ambiguity in biological sex, and a person's legal rights and social status can be heavily influenced by whether their birth certificate says male or female.

“The main problem with a strong dichotomy is that there are intermediate cases that push the limits and ask us to figure out exactly where the dividing line is between males and females,” says Arthur Arnold at the University of California, Los Angeles, who studies biological sex differences. “And that's often a very difficult problem, because sex can be defined a number of ways.”

**The start of sex**

That the two sexes are physically different is obvious, but at the start of life, it is not. Five weeks into development, a human embryo has the potential to form both male and female anatomy. Next to the developing kidneys, two bulges known as the gonadal ridges emerge alongside two pairs of ducts, one of which can form the uterus and Fallopian tubes, and the other the male internal genital plumbing: the epididymes, vas deferentia and seminal vesicles. At six weeks, the gonad switches on the developmental pathway to become an ovary or a testis. If a testis develops, it secretes testosterone, which supports the development of the male ducts. It also makes other hormones that force the presumptive uterus and Fallopian tubes to shrink away. If the gonad becomes an ovary, it makes oestrogen, and the lack of testosterone causes the male plumbing to wither. The sex hormones also dictate the development of the external genitalia, and they come into play once more at puberty, triggering the development of secondary sexual characteristics such as breasts or facial hair.

Changes to any of these processes can have dramatic effects on an individual's sex. Gene mutations affecting gonad development can result in a person with XY chromosomes developing typically female characteristics, whereas alterations in hormone signalling can cause XX individuals to develop along male lines.

For many years, scientists believed that female development was the default programme, and that male development was actively switched on by the presence of a particular gene on the Y chromosome. In 1990, researchers made headlines when they uncovered the identity of this gene[3](http://www.nature.com/news/sex-redefined-1.16943#b3), [4](http://www.nature.com/news/sex-redefined-1.16943#b4), which they called *SRY*. Just by itself, this gene can switch the gonad from ovarian to testicular development. For example, XX individuals who carry a fragment of the Y chromosome that contains *SRY* develop as males.

By the turn of the millennium, however, the idea of femaleness being a passive default option had been toppled by the discovery of genes that actively promote ovarian development and suppress the testicular programme — such as one called *WNT4*. XY individuals with extra copies of this gene can develop atypical genitals and gonads, and a rudimentary uterus and Fallopian tubes[5](http://www.nature.com/news/sex-redefined-1.16943#b5). In 2011, researchers showed[6](http://www.nature.com/news/sex-redefined-1.16943#b6) that if another key ovarian gene, *RSPO1*, is not working normally, it causes XX people to develop an ovotestis — a gonad with areas of both ovarian and testicular development.

These discoveries have pointed to a complex process of sex determination, in which the identity of the gonad emerges from a contest between two opposing networks of gene activity. Changes in the activity or amounts of molecules (such as WNT4) in the networks can tip the balance towards or away from the sex seemingly spelled out by the chromosomes. “It has been, in a sense, a philosophical change in our way of looking at sex; that it's a balance,” says Eric Vilain, a clinician and the director of the Center for Gender-Based Biology at the University of California, Los Angeles. “It's more of a systems-biology view of the world of sex.”

**Battle of the sexes**

According to some scientists, that balance can shift long after development is over. Studies in mice suggest that the gonad teeters between being male and female throughout life, its identity requiring constant maintenance. In 2009, researchers reported[7](http://www.nature.com/news/sex-redefined-1.16943#b7) deactivating an ovarian gene called *Foxl2* in adult female mice; they found that the granulosa cells that support the development of eggs transformed into Sertoli cells, which support sperm development. Two years later, a separate team showed[8](http://www.nature.com/news/sex-redefined-1.16943#b8) the opposite: that inactivating a gene called *Dmrt1* could turn adult testicular cells into ovarian ones. “That was the big shock, the fact that it was going on post-natally,” says Vincent Harley, a geneticist who studies gonad development at the MIMR-PHI Institute for Medical Research in Melbourne.

The gonad is not the only source of diversity in sex. A number of DSDs are caused by changes in the machinery that responds to hormonal signals from the gonads and other glands. Complete androgen insensitivity syndrome, or CAIS, for example, arises when a person's cells are deaf to male sex hormones, usually because the receptors that respond to the hormones are not working. People with CAIS have Y chromosomes and internal testes, but their external genitalia are female, and they develop as females at puberty.

Conditions such as these meet the medical definition of DSDs, in which an individual's anatomical sex seems to be at odds with their chromosomal or gonadal sex. But they are rare — affecting about 1 in 4,500 people[9](http://www.nature.com/news/sex-redefined-1.16943#b9). Some researchers now say that the definition should be widened to include subtle variations of anatomy such as mild hypospadias, in which a man's urethral opening is on the underside of his penis rather than at the tip. The most inclusive definitions point to the figure of 1 in 100 people having some form of DSD, says Vilain (see ['The sex spectrum'](http://www.nature.com/news/sex-redefined-1.16943#spectrum)).

**The sex spectrum**

| A typical male has XY chromosomes, and a typical female has XX. But owing to genetic variation or chance events in development, some people do not fit neatly into either category. Some are classed as having differences or disorders of sex development (DSDs), in which their sex chromosomes do not match their sexual anatomy. |
| --- |
|  | **Chromosomes** | **Gonads** | **Genitals** | **Other characteristics/ examples** |
| **Typical male** | XY | Testes | Male internal and external genitals | Male secondary sexual characteristics |
| **Subtle variations** | XY | Testes | Male internal and external genitals | Subtle differences such as low sperm production. Some caused by variation in sex-development genes. |
| **Moderate variations** | XY | Testes | Male external genitals with anatomical variations such as urethral opening on underside of penis. | Affects 1 in 250–400 births. |
| **46,XY DSD** | XY | Testes | Often ambiguous | The hormonal disorder persistent Müllerian duct syndrome results in male external genitals and testes, but also a womb and Fallopian tubes. |
| **Ovotesticular DSD** | XX, XY or mix of both | Both ovarian and testicular tissue | Ambiguous | Rare reports of predominantly XY people conceiving and bearing a healthy child. |
| **46,XX testicular DSD** | XX | Small testes | Male external genitals | Usually caused by presence of male sex-determining gene *SRY*. |
| **Moderate variations** | XX | Ovaries | Female internal and external genitals | Variations in sex development such as premature shutdown of ovaries. Some caused by variation in sex-development genes. |
| **Subtle variations** | XX | Ovaries | Female internal and external genitals | Subtle differences such as excess male sex hormones or polycystic ovaries. |
| **Typical female** | XX | Ovaries | Female internal and external genitals | Female secondary sexual characteristics |

But beyond this, there could be even more variation. Since the 1990s, researchers have identified more than 25 genes involved in DSDs, and next-generation DNA sequencing in the past few years has uncovered a wide range of variations in these genes that have mild effects on individuals, rather than causing DSDs. “Biologically, it's a spectrum,” says Vilain.

A DSD called congenital adrenal hyperplasia (CAH), for example, causes the body to produce excessive amounts of male sex hormones; XX individuals with this condition are born with ambiguous genitalia (an enlarged clitoris and fused labia that resemble a scrotum). It is usually caused by a severe deficiency in an enzyme called 21-hydroxylase. But women carrying mutations that result in a milder deficiency develop a 'non-classical' form of CAH, which affects about 1 in 1,000 individuals; they may have male-like facial and body hair, irregular periods or fertility problems — or they might have no obvious symptoms at all. Another gene, *NR5A1*, is currently fascinating researchers because variations in it cause a wide range of effects[10](http://www.nature.com/news/sex-redefined-1.16943#b10), from underdeveloped gonads to mild hypospadias in men, and premature menopause in women.

Many people never discover their condition unless they seek help for infertility, or discover it through some other brush with medicine. Last year, for example, surgeons reported that they had been operating on a hernia in a man, when they discovered that he had a womb[11](http://www.nature.com/news/sex-redefined-1.16943#b11). The man was 70, and had fathered four children.

**Cellular sex**

Studies of DSDs have shown that sex is no simple dichotomy. But things become even more complex when scientists zoom in to look at individual cells. The common assumption that every cell contains the same set of genes is untrue. Some people have mosaicism: they develop from a single fertilized egg but become a patchwork of cells with different genetic make-ups. This can happen when sex chromosomes are doled out unevenly between dividing cells during early embryonic development. For example, an embryo that starts off as XY can lose a Y chromosome from a subset of its cells. If most cells end up as XY, the result is a physically typical male, but if most cells are X, the result is a female with a condition called Turner's syndrome, which tends to result in restricted height and underdeveloped ovaries. This kind of mosaicism is rare, affecting about 1 in 15,000 people.

The effects of sex-chromosome mosaicism range from the prosaic to the extraordinary. A few cases have been documented in which a mosaic XXY embryo became a mix of two cell types — some with two X chromosomes and some with two Xs and a Y — and then split early in development[12](http://www.nature.com/news/sex-redefined-1.16943#b12). This results in 'identical' twins of different sexes.

There is a second way in which a person can end up with cells of different chromosomal sexes. James's patient was a chimaera: a person who develops from a mixture of two fertilized eggs, usually owing to a merger between embryonic twins in the womb. This kind of chimaerism resulting in a DSD is extremely rare, representing about 1% of all DSD cases.

“Surgeons discovered that the man had a womb. He was 70.”

Another form of chimaerism, however, is now known to be widespread. Termed microchimaerism, it happens when stem cells from a fetus cross the placenta into the mother's body, and vice versa. It was first identified in the early 1970s — but the big surprise came more than two decades later, when researchers discovered how long these crossover cells survive, even though they are foreign tissue that the body should, in theory, reject. A study in 1996 recorded women with fetal cells in their blood as many as 27 years after giving birth[13](http://www.nature.com/news/sex-redefined-1.16943#b13); another found that maternal cells remain in children up to adulthood[14](http://www.nature.com/news/sex-redefined-1.16943#b14). This type of work has further blurred the sex divide, because it means that men often carry cells from their mothers, and women who have been pregnant with a male fetus can carry a smattering of its discarded cells.

Microchimaeric cells have been found in many tissues. In 2012, for example, immunologist Lee Nelson and her team at the University of Washington in Seattle found XY cells in post-mortem samples of women's brains[15](http://www.nature.com/news/sex-redefined-1.16943#b15). The oldest woman carrying male DNA was 94 years old. Other studies have shown that these immigrant cells are not idle; they integrate into their new environment and acquire specialized functions, including (in mice at least) forming neurons in the brain[16](http://www.nature.com/news/sex-redefined-1.16943#b16). But what is not known is how a peppering of male cells in a female, or vice versa, affects the health or characteristics of a tissue — for example, whether it makes the tissue more susceptible to diseases more common in the opposite sex. “I think that's a great question,” says Nelson, “and it is essentially entirely unaddressed.” In terms of human behaviour, the consensus is that a few male microchimaeric cells in the brain seem unlikely to have a major effect on a woman.

Scientists are now finding that XX and XY cells behave in different ways, and that this can be independent of the action of sex hormones. “To tell you the truth, it's actually kind of surprising how big an effect of sex chromosomes we've been able to see,” says Arnold. He and his colleagues have shown[17](http://www.nature.com/news/sex-redefined-1.16943#b17) that the dose of X chromosomes in a mouse's body can affect its metabolism, and studies in a lab dish suggest[18](http://www.nature.com/news/sex-redefined-1.16943#b18) that XX and XY cells behave differently on a molecular level, for example with different metabolic responses to stress. The next challenge, says Arnold, is to uncover the mechanisms. His team is studying the handful of X-chromosome genes now known to be more active in females than in males. “I actually think that there are more sex differences than we know of,” says Arnold.

**Beyond the binary**

Biologists may have been building a more nuanced view of sex, but society has yet to catch up. True, more than half a century of activism from members of the lesbian, gay, bisexual and transgender community has softened social attitudes to sexual orientation and gender. Many societies are now comfortable with men and women crossing conventional societal boundaries in their choice of appearance, career and sexual partner. But when it comes to sex, there is still intense social pressure to conform to the binary model.

This pressure has meant that people born with clear DSDs often undergo surgery to 'normalize' their genitals. Such surgery is controversial because it is usually performed on babies, who are too young to consent, and risks assigning a sex at odds with the child's ultimate gender identity — their sense of their own gender. Intersex advocacy groups have therefore argued that doctors and parents should at least wait until a child is old enough to communicate their gender identity, which typically manifests around the age of three, or old enough to decide whether they want surgery at all.

This issue was brought into focus by a lawsuit filed in South Carolina in May 2013 by the adoptive parents of a child known as MC, who was born with ovotesticular DSD, a condition that produces ambiguous genitalia and gonads with both ovarian and testicular tissue. When MC was 16 months old, doctors performed surgery to assign the child as female — but MC, who is now eight years old, went on to develop a male gender identity. Because he was in state care at the time of his treatment, the lawsuit alleged not only that the surgery constituted medical malpractice, but also that the state denied him his constitutional right to bodily integrity and his right to reproduce. Last month, a court decision prevented the federal case from going to trial, but a state case is ongoing.

“This is potentially a critically important decision for children born with intersex traits,” says Julie Greenberg, a specialist in legal issues relating to gender and sex at Thomas Jefferson School of Law in San Diego, California. The suit will hopefully encourage doctors in the United States to refrain from performing operations on infants with DSDs when there are questions about their medical necessity, she says. It could raise awareness about “the emotional and physical struggles intersex people are forced to endure because doctors wanted to 'help' us fit in,” says Georgiann Davis, a sociologist who studies issues surrounding intersex traits and gender at the University of Nevada, Las Vegas, who was born with CAIS.

Doctors and scientists are sympathetic to these concerns, but the MC case also makes some uneasy — because they know how much is still to be learned about the biology of sex[19](http://www.nature.com/news/sex-redefined-1.16943#b19). They think that changing medical practice by legal ruling is not ideal, and would like to see more data collected on outcomes such as quality of life and sexual function to help decide the best course of action for people with DSDs — something that researchers are starting to do.

Diagnoses of DSDs once relied on hormone tests, anatomical inspections and imaging, followed by painstaking tests of one gene at a time. Now, advances in genetic techniques mean that teams can analyse multiple genes at once, aiming straight for a genetic diagnosis and making the process less stressful for families. Vilain, for example, is using whole-exome sequencing — which sequences the protein-coding regions of a person's entire genome — on XY people with DSDs. Last year, his team showed[20](http://www.nature.com/news/sex-redefined-1.16943#b20) that exome sequencing could offer a probable diagnosis in 35% of the study participants whose genetic cause had been unknown.

Vilain, Harley and Achermann say that doctors are taking an increasingly circumspect attitude to genital surgery. Children with DSDs are treated by multidisciplinary teams that aim to tailor management and support to each individual and their family, but this usually involves raising a child as male or female even if no surgery is done. Scientists and advocacy groups mostly agree on this, says Vilain: “It might be difficult for children to be raised in a gender that just does not exist out there.” In most countries, it is legally impossible to be anything but male or female.

Yet if biologists continue to show that sex is a spectrum, then society and state will have to grapple with the consequences, and work out where and how to draw the line. Many transgender and intersex activists dream of a world where a person's sex or gender is irrelevant. Although some governments are moving in this direction, Greenberg is pessimistic about the prospects of realizing this dream — in the United States, at least. “I think to get rid of gender markers altogether or to allow a third, indeterminate marker, is going to be difficult.”

So if the law requires that a person is male or female, should that sex be assigned by anatomy, hormones, cells or chromosomes, and what should be done if they clash? “My feeling is that since there is not one biological parameter that takes over every other parameter, at the end of the day, gender identity seems to be the most reasonable parameter,” says Vilain. In other words, if you want to know whether someone is male or female, it may be best just to ask.

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**Comments for this thread are now closed.**

**14 comments**

1. 

*oliver elbs* • 2015-02-28 03:09 PM

This article may be as important as the invention of (matriarchal) agriculture 10000 years ago - and may be as important as the discoveries of Gregor Mendel exactly 150 years ago. Maybe for the first time in human history -- since the time of the egalitarian hunter-gatherers, who did not bother about inheritance problems at all (i.e., horticulture, agriculture, animal breeding, matrilinearity, patrilinearity, history, evolutionary biology, genetics) -- the definition of "mother" is not dependent any more on violent terms like "men"/"women"/"male"/"female"/"XY"/etc. For the first time, non-violent communication (Marshall B. Rosenberg, died on February 7, 2015) and a non-violent language is possible. Matriarchal theorists (like Heide Göttner-Abendroth) should definitely reconsider their (lacking) definition of what a "mother" is: a (human etc.) being giving birth to another (human etc.) being. This definition is not dependent on "male"/"female" etc. any more. Now, everything is possible again (despite the still prevailing patriarchalisms world-wide) -- and even "parthenogenesis" (as in the old myths of humanity, e.g., the Trobriand Islanders) may be fully conceivable...

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*Stephanie Sometimes* • 2015-02-26 04:18 PM

Thanks for this article. I am a transgendered woman, who is doing a Masters degree in Theology, specializing in gender. It is fascinating that scientists are now discovering things that challenge the traditional construct of gender. See 'Hermaphrodites and the Medical invention of sex' http://www.hup.harvard.edu/catalog.php?isbn=9780674001893 Warm regards, Stephanie

1. 

*Tom Perkins* • 2015-02-26 01:36 PM

"Doctors and scientists are sympathetic to these concerns... — something that researchers are starting to do." This comes across as if until they know what they are doing, they want to keep on doing what they want to do! The old joke about the difference between God and doctor's is that God doesn't think he's a doctor... It would seem to be an article more cognizant of reality, if it were to emphasize that the vast majority of people are simply male and female, and are fine with that. A corollary of Occam's Razor; edge cases should not be magnified unnecessarily.

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*B Love* • 2015-02-25 10:08 PM

I think the main problem the issue is with the people trying to push an agenda one way ot the other. For instance, just because a mother who had a male child carries some of his male genes for some time afterward, it in no way influences who she is or changes her overall genetic makeup in a way one would need to be confused about what sex she is genetically. The same with a male child carrying some of his mothers DNA. That is a silly argument meant to confuse people where no confusion is necessary. Someone born with rudimentary female or male sex organs that haven't developed, but already have fully developed sex organs of either male or female obviously were meant to be whatever sex that sex organ was that was more developed. The genetic remnants of whatever mutation didn't develop fully should be removed surgically. In cases where there isn't a clear distinction, someone needs to decide within the first few weeks of birth what to do in terms of which sexual organs are kept and removed. Better yet, they should be able to test in the womb if this genetic defect is going to play a prominent role so the parents can decide to abort the pregnancy or not the same way they might in any other case of genetic defect. The only difficulty here is that the wrong people are trying to influence how people should think on this issue. It isn't the researchers’ job to push these kinds of issues. That steps out of the realm of science, and becomes scientism which is when someone applying science in a way that goes far beyond what the science proves disguised as pure science. Issues like abortion are purely religious and while the Bible may remotely touch on the subject, it doesn't touch on it in cases of genetic defect. Both sides can fight that out on philosophical terms. But in any case, there is no reason to let anyone carry two sets of sexual organs. That can only cause difficulties physically and mentally the human body wasn't designed to handle. The influx of too many of any kind of hormones that aren't usually there in such large numbers because of two sets of sexual organs, both male and female, will logically influence all sorts of abnormal behaviors not dealt with by people with one clear set of male or female sexual organs. The article tries to overlook this obvious problem pretending it isn't something they need to contend with because anything that happens naturally is good in their overly simplified biased eyes. In nature, such genetic malformations mean a normal member of the species was selected for extinction. As humans we can intervene and help fix the genetic mutation influence by removing as much of the conflicting influence as possible. Only in cases where there isn't a clear and obvious distinction of one sexual organ being more developed over the other should anyone be allowed to decide against what was clearly more developed. Much of the mental confusion in a person about their sexual orientation can be removed the sooner this is decisively dealt with as soon as possible from birth under those terms. For adults, the hormones that hold sway over their confusion will be greatly diminished if the same sets of decision parameters are used. In other words, don't leave it up to the individual if there is a clear and obvious set of developed sexual organs already in existence over a set that aren't developed as well. Remove the undeveloped sexual organs and much of the hormonal influence that causes confusion will be alleviated by the simple fact those hormones will no longer hold much, if any, sway over their thoughts and desires. It really isn't that difficult in most cases. It isn't nearly as confusing as the article tries to make it.

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*Claire Ainsworth* • 2015-02-25 11:27 AM

@ Laura Viney Thank you for raising an important issue. The naming and definition of intersex or differences/ disorders of sex development (DSDs) is a sensitive topic. Some people dislike the term “intersex” because they say it implies that people with these conditions are in some sort of “in between” state. Others object to the term “disorder”, saying it implies the bodies of affected people are wrong and in need of medical intervention; they prefer the term “differences” or “variations” in sex development, or indeed, the term “intersex” or “intersex traits”. Doctors treating a baby with severe 21-hydroxylase deficiency, which causes life-threatening adrenal gland problems, would, however, argue that this is more than a variation in typical physiology and that the term “disorder” is appropriate. My use of the different terms, where appropriate in the text, is to reflect these different points of view. The term “disorders of sex development” was created in 2006 to address a number of concerns surrounding the previous nomenclature of these conditions, and is now widely used in the biomedical literature: please see ref 9 in the story--the Consensus Statement on the Management of Intersex Disorders (and refs therein). The definition of DSD in the Consensus statement can be interpreted in different ways, which accounts for the numbers cited in my story.

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*Claire Ainsworth* • 2015-02-25 11:12 AM

@ Charin Davenport Thank you for your comment. My story is not an academic review, which would involve comprehensive literature citation, but a piece of journalism, which focuses on the reporting of current events relating to the public interest.

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*Laura Viney* • 2015-02-22 05:42 AM

Unfortunately, this author has misinterpreted some of the original source material for the statistics in this article. This article states "intersex conditions, or differences or disorders of sex development (DSDs) — often face difficult decisions about whether to bring up their child as a boy or a girl. Some researchers now say that as many as 1 person in 100 has some form of DSD." However, DSD is not the same as intersex, it includes far more conditions that just intersex, including differences in genital size which by no means would cause a parent to question the sex of its child. The original German study (which this article traces back to) "estimates a rate of 2.2/10 000 cases with ambiguous genitalia at birth". With the correct statistics, I believe sex can still be considered binary, with a few exceptions. Gender, however, it more of a social construct and seems to be the more fluid concept. http://www.biomedcentral.com/1471-2458/9/110

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*Charin Davenport* • 2015-02-22 03:54 AM

In my Advanced Composition: Gender and Culture course, my students will have the option of reading "The Five Sexes" and "The Five Sexes: Revisited," as well as this article and the comments. It is unfortunate, to say the least, that Anne Fausto-Sterling's work was not cited; on the other hand, thank you for providing my students with the opportunity to see firsthand why it is so important to credit your sources appropriately and to never settle for the first and second layer of research. Whenever possible, I tell them, go to the original sources, which In this case would have been the A F-S essays and the hard work of so many intersex activists. BTW -- I am a trans\* part-time professor at two colleges (the first trans\* professor at both schools).

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*anne Fausto-sterling* • 2015-02-20 02:17 PM

I thank Helen Pearson and the author for their responses, but I don't agree with their choices. It would not have been hard to create a hyperlinked box that showed the origins of these ideas. Giving credit and showing chains of knowledge are part of doing science journalism in an ethical and professional manner. It does a disservice to science to pretend that all the ideas come from scientists in the current moment. The ideas in this article come from intersex activists (many of whom some of the scientists you do cite knew and worked with) as well as historians of science and biologists such as myself. Feminist theory also contributed to the growth of these ideas. Biology is not an island divorced from the rest of academia or society. It is not great journalism to pretend otherwise.

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*Michelle Sarine* • 2015-02-20 01:52 PM

So, the vast majority of people are 46, XX and 46, XY. Sometimes there are errors and these cause a number of problems for the people concerned, but instead of this fact proving the rule that we have two sexes and that humans sexually reproduce, it's a spectrum? That's rather confusing, rarely also humans can be born with upper or lower limb reduction defects, but then we wouldn't go on to say having 4 limbs is a spectrum and this doesn't seem to be considered to be redefining the human phenotype at all. All this really proves is that, in biological terms, there are a number of markers that determine sex in an individual. There isn't a third sex, no chromosome Z, but rather X and Y and those determine sex unless something else happens. Realistically, it's not that hard to determine the sex of a person. In most cases, a female is objectively that and a male also and we can tell them apart readily even before the social context comes in, and even if you only find skeletal remains. It only rarely becomes a complex thing, and where intersex conditions occur it's quite clear that unless the need for surgery or other intervention is present and urgent, it's best to let the individual themselves decide how they feel and what they want to do about it. Socially, I think there can some concerns about a world where sex is made irrelevant particularly for females, as biology does count and erasing this could have significant impact for specific accomodations they need, such as when pregnant. If you look at such issues as sex-selective abortions of female fetuses for instance, sex very much counts. So much so there are millions of missing females.

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*Helen Pearson* • 2015-02-19 07:20 PM

Thanks for your useful comments on this story, which I edited. The author and I are aware there is a long history of discussion and research about DSDs and about the idea of sex spanning a spectrum. Space constraints meant that we were unable to delve deeply into the history -- and our aim here was to highlight some of the more recent developments in genetics and other biological sciences, which are showing that the complexity of sex is greater than was once thought.

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*Christian Munthe* • 2015-02-19 10:52 AM

As Anne F-S, I'm happy that mainstream biology seems to be finally catching up with already longstanding work, although slightly dismayed by the lack of recognition of forerunners and – thereby – overstatement of novelty/originality. At the same time, it is a constructive development that what seems to be mostly ideological/moralistic orthodoxy with regard to, especially human, sexuality is finally starting to take its leave out of biological scientific taxonomy and theory. To facilitate further work in this direction, I humbly point to a sketch of a continuous quatitative model of sexes (as well as genders and sexual orientations), presented a few years back: [A Continuous Quantitative Theory of Sex, Gender and Sexuality](http://philosophicalcomment.blogspot.se/2011/05/continuous-quantitative-theory-of-sex.html), url: http://philosophicalcomment.blogspot.se/2011/05/continuous-quantitative-theory-of-sex.html This model would seem to facilitate perfectly the "spectrum" idea of sexes (and other things), in particular, it allows for any type of future extension or specification of this idea in light of enrichened and refined empirical data.

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*anne Fausto-sterling* • 2015-02-18 06:38 PM

Am glad that other biologists have discovered what I and other scholars and intersex activists started writing about in the early 1990s. Too bad Ainsworth did not see fit to recognize or cite any of this work, including Blackless et al, the only systematic attempt to figure out the incidence of various forms of intersex. Vilain cites our data in the article but does not acknowledge us. Erasure works in fascinating ways. For more see The 5 Sexes, The 5 Sexes Revisited, Sexing the Body, and Sarah Richardson's Sex Itself. My articles can be found on researchgate.net

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*Anand CV* • 2015-02-18 04:58 PM

I had this hunch that there is a connection between chaotic bifurcation and evolution of sexes. It is rather abstract idea, but the hunch is strong and hence sharing here. The prediction of such a hypothesis is the evolution of non-binary sexes. https://anandcv.wordpress.com/2012/01/24/chaos-theory-and-the-evolution-of-sexes/ Anybody think this is serious?