

# STUCK IN THE MIDDLE

**Eric Vilain** built a career studying aspects of sex that make some people uncomfortable. Now things are getting uncomfortable for him.

BY SARA REARDON

As a medical student in Paris in the 1980s, Eric Vilain found himself pondering the differences between men and women. What causes them to develop differently, and what happens when the process goes awry? At the time, he was encountering babies that defied simple classification as a boy or girl. Born with disorders of sex development (DSDs), many had intermediate genitalia — an overlarge clitoris, an undersized penis or features of both sexes.

Then, as now, the usual practice was to operate. And the decision of whether a child would be left with male or female genitalia was often made not on scientific evidence, says Vilain, but on practicality: an oft-repeated, if insensitive, line has it that “it’s easier to dig a hole than build a pole”. Vilain found the approach disturbing. “I was fascinated and shocked by how the medical team was making decisions.”

Vilain has spent the better part of his career studying the ambiguities of sex. Now a paediatrician and geneticist at the University of California, Los Angeles (UCLA), he is one of the world’s foremost experts on the genetic determinants of DSDs. He has worked closely with intersex advocacy groups that campaign for recognition and better medical treatment — a movement that has recently gained momentum.

And in 2011, he established a major longitudinal study to track the psychological and medical well-being of hundreds of children with DSDs.

Vilain says that he doesn’t seek out controversy, but his research seems to attract it. His studies on the genetics of sexual orientation — an area that few others will touch — have attracted criticism from scientists, gay-rights activists and conservative groups alike. He is also a medical adviser for the International Olympic Committee, which about five years ago set controversial rules by which intersex individuals are allowed to compete in women’s categories.

But what has brought Vilain the most grief of late has been his stance on sex-assignment surgery for infants with DSDs. Although he generally opposes it, he won’t categorically condemn it or the doctors who perform it. As a result, many intersex advocates who object to the practice now see him as a hindrance to their cause. In November, nine bioethicists and activists resigned as advisers to his longitudinal study in protest. “I just lost my patience,” says Alice Dreger, a bioethicist who used to work at Northwestern University in Evanston, Illinois, and who was among the first to leave the study.

Although dismayed by their departure, Vilain refuses to take a stance until it is supported by

science. “The thing I don’t want to compromise is scientific integrity, even when it clashes with the community narrative.”

## BREAKING BINARY

The idea that there are only two sexes is so entrenched in society that the first question many people ask on finding out that a friend is pregnant is: boy or girl? “People don’t answer ‘I’m having a baby,’” says Vilain. “They probably should.”

At Necker University Hospital for Sick Children in Paris in the 1980s, he says, doctors presumed that a child would be psychologically damaged if he or she did not have normal-looking genitalia. In Vilain’s experience, that belief was so strong that doctors would take genital abnormalities into account when deciding how

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hard to fight to save a premature baby. “The unanimous feeling was that boys with a micropenis could never achieve a normal life — that they were doomed,” he says. (The paediatric-surgery department at Necker refused to answer questions relating to past or current standards of care.)

DSDs occur in an estimated 1–2% of live births, and hundreds of genital surgeries are performed on infants around the world every year<sup>1</sup>. But there are no estimates as to how often a child’s surgically assigned sex ends up different from the gender they come to identify with.

What do exist, however, are stories of people who say that they have been harmed: children who struggle to fit in with peers, adolescents who are stressed, harassed or attempt suicide, and adults who are furious that they were not

involved in the decision to modify their bodies. Over the past two decades, and especially in the past few years, intersex activists worldwide — some of whom do not identify as either gender — have begun to speak out against the practice. Unless a child’s life is in danger, they argue, he or she should have the right to decide on surgery when older.

Vilain’s fascination with the biological complexities of sexual differentiation made him want to study the causes of DSDs. So in 1990, he joined the lab of geneticist Marc Fellous at the Pasteur Institute in Paris. Fellous was studying a newly discovered gene called *SRY*, which resides on the Y chromosome and is crucial in triggering the development of male features. Vilain helped to identify the causes of several DSDs, such as XY people who look female because

of mutations that disable the *SRY* gene<sup>2</sup>, and people who carry a copy of *SRY* even if they do not have a Y chromosome<sup>3</sup>. Vilain was an unusual student, Fellous says, because his clinical background allowed him to bridge lab work and patient care. Fellous says that it is often difficult to explain to the families of children with DSDs why the research would be helpful. “Eric was useful for this,” he says. “He was a very open mind, really close to families.”

In 1995, Vilain left France for a faculty job at UCLA. There, he began tackling questions about sexual development from every possible angle. He created mouse models with mutations in *SRY* or other sex-linked genes to study how their developing brains respond to hormones — research that could lead to better care for people with DSDs.



Perhaps most notoriously, he has explored the roots of sexual orientation, work that made even his colleagues uncomfortable. In 2006, he was looking to publish work by his postdoc Sven Bocklandt, who had found links between the way genes are expressed from a mother's X chromosomes and the chances of her having a gay son. When he approached biostatisticians for help, several refused to collaborate, Vilain says, because they were afraid of how the public might respond.

Studies on the genetic underpinnings of homosexuality are controversial. Religious conservatives who believe that being gay is a choice argue that scientists are trying to legitimize it; gay activists worry that the research will lead to misguided attempts to 'cure' gay people. Vilain gets occasional attacks from both groups. But he says that his colleagues' squeamishness around controversial research was unscientific. So, he stormed into the office of the UCLA biostatistics chair, Kenneth Lange, to complain.

"Eric's not afraid to kick up some dust and stand up for the people in his lab," Bocklandt says. "I think that's why he's been so successful." A statistician eventually volunteered to help.

Dean Hamer, a retired geneticist formerly at the US National Cancer Institute in Bethesda, Maryland, trained Bocklandt and has studied the genetics of sexual orientation. He says that Vilain is pretty much the only geneticist who still does serious research on the topic. "That takes a level of courage and belief that ultimately the biology will win out," he says.

#### COURTING ADVOCACY

Vilain's research and interest in policy has put him on the front lines of the lesbian, gay, bisexual, transgender and queer (LGBTQ) rights movement and has made his lab a magnet for LGBTQ students. His work also made him a sort of scientist-laureate for the intersex advocacy community, which started gaining prominence in the early 1990s with the formation of the Intersex Society of North America in Rohnert Park, California. The group, founded by activist Bo Laurent, lobbied for recognition of intersex as a human condition rather than an affliction, and opposed infant surgery.

Vilain, who met Laurent in 1997, says that she helped to shape his opinions on surgery and other topics that are important to intersex people, such as the stigma they face. Although Laurent and her colleagues were well informed and knowledgeable about the science of DSDs, they struggled to be heard in scientific conversations. "I think the view was that they were zealots," Vilain recalls.

In 2005, several paediatric societies met in Chicago to draft a consensus statement on the management of intersex conditions — a still-influential document<sup>4</sup> that guides the standard

of care. Laurent attended the meeting hoping to see the word hermaphrodite struck from the medical vocabulary. The term was not only offensive — it labelled a person rather than a disorder — it was also scientifically inaccurate because it suggested that the person had functioning male and female organs.

Rather than being heard, Laurent recalls being sidelined. But Vilain, who headed the genetics working group, met with her in secret throughout the meeting, drafting a case to present to the group. They met stiff opposition from medical doctors, who saw no reason for change, but their language was ultimately adopted in the final statement<sup>4</sup>.

Over the years, Vilain continued to build a reputation as an ally to intersex people. In 2011, when he and psychologist David Sandberg at the University of Michigan in Ann Arbor began the ten-institution registry to track children with DSDs, ethicists and activists enthusiastically joined its advisory board. Funded by the US National Institutes of Health, the Disorders of Sex Development Translational Research Network has enrolled more than 300 children, collecting medical records and blood samples and performing interviews to answer a variety of biological and psychological questions.

Many of the advocates who joined as advisers had hoped that development of the network would lead to a denouncement of infant genital surgery by revealing the damage that it can cause. "No one has demonstrated anything but harm," says Anne Tamar-Mattis, legal director of the intersex advocacy group interACT in San Francisco, California. "Research that settles that question is useful."

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But the study has yet to do what advocates hoped. Sandberg, who heads the network's psychological research, has collected evidence that emotional and social support from the family is the most important contributor to the psychological and mental health of a child with a DSD. He suspects that it has an even greater impact than surgery. "I never question people's experiences," Sandberg says of the activists who believe that surgery is always harmful. "What I do question is whether they're generalizable."

One argument in favour of infant surgery is that a child could be psychologically scarred by growing up with intermediate genitalia, but there is little evidence for or against that. In rare

cases, surgery could help to prevent cancer. Complete androgen insensitivity syndrome, for instance, confers an increased risk of testicular cancer that can be lowered through surgery<sup>5</sup>. But Vilain points out that the risk before puberty is very small<sup>6</sup>, suggesting that surgery could wait.

Although few surgeons were willing to talk openly about infant genital surgery, some do argue that the fear of harm is overblown or at least outdated. Laurence Baskin, a paediatric urologist at the University of California, San Francisco, says that the days of "assigning gender" are long gone, because scientists no longer believe that a child can be made to be a boy or a girl. Most DSDs can be diagnosed and the outcomes predicted; physicians use the diagnosis to advise parents on which gender the child is likely to identify with, he says. For instance, the most common cause for a DSD is congenital adrenal hyperplasia — which can result in ambiguous genitalia for XX children. Between 90% and 95% of people with the condition identify as female<sup>7</sup>.

When asked about children with this disorder who ultimately do not identify as female, another paediatric urologist — who wished not to be named — argues that the process can be reversed. People have sex-change surgery as adults all the time, he says.

Such arguments infuriate Tamar-Mattis. "If one time in 20 you're cutting a little boy's penis off, is that a risk worth taking?" she says.

Vilain doesn't think so, and doesn't generally recommend surgery to his patients. He says that in his experience, more parents are now choosing to delay surgery.

But he and his collaborators on the longitudinal study are reluctant to condemn surgery outright — they prefer to approach each case individually and to consider the views of parents who may feel strongly about what is right for their child.

This attitude helped to create the rift between the researchers and intersex advocates. At the end of 2015, Dreger, who had served as the bioethicist for the longitudinal study announced her resignation in a blogpost. "I can't continue to help develop 'conversations' around 'shared decision making' that allow decisions to be made that I believe violate the most basic rights of these children," she wrote. "I am fed up with being asked to be a sort of absolving priest of the medical establishment."

Vilain was blind-sided by the post. "I was very saddened by this," he says. "She's a friend." After her departure, eight other advocates sent the study's leaders a letter of resignation.

Most would not comment on the record, but say that they were upset that the researchers were making decisions about which questions to pursue without sufficiently consulting them.



The controversy surrounding female runner Caster Semenya's participation in international competitions helped lead to rule changes about who can compete in women's events.

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For example, advocates are also concerned about the psychological impacts on children from having their genitals photographed for the purpose of diagnosis or to plan treatment. Some say that Vilain became hostile in meetings. They accuse him and Sandberg of putting research interests ahead of human suffering.

"We live in a community of people who have experienced the harms of these practices," says Arlene Baratz, a radiologist who serves as medical adviser to a DSD support group and is one of those who resigned from the study. She and others say that in their decades of work as advocates they have never been contacted by someone who was helped by surgery.

Vilain says that he does talk to such patients in his practice, but because they are living happy lives, they have no reason to speak out. Without data on outcomes, says Douglas Diekema, a medical ethicist at the Seattle Children's Research Hospital Institute in Washington, it is impossible to weigh up whether surgery is overall harmful, helpful or neutral for most people. "Good ethics requires good data," he says.

But a legal battle in the United States could change medical practice before those data are in. Tamar-Mattis is one of the lawyers representing the family of a baby who underwent feminizing surgery at 16 months old. The child, now 11 years old, identifies as male, and his lawyers argue that South Carolina's Department of Social Services and the university that performed the surgery violated the child's rights.

Intersex advocates are watching the case with great interest, because it could lay the groundwork for future suits that could effectively

outlaw the procedures in the United States.

In January, the United Nations released a report saying that sex-assignment surgeries on infants "lead to severe and life-long physical and mental pain and suffering and can amount to torture and ill-treatment". Vilain and Sandberg worry that the language could alienate doctors and parents alike. "You're basically calling doctors torturers when they're doing something considered standard medical practice," Vilain says. He points out that few medical procedures are governed by law — physicians tend to operate according to guidelines and principles. "I'm not opposed to guidelines, I'm opposed to things that completely alter medical practice in an irreversible way," he says. He and Sandberg also worry that legal bans could drive infant surgery underground. "Parents are scared. You just don't dictate to them and say get over it," Sandberg says.

#### TESTING PATIENCE

Vilain's expertise has plunged him into other controversies. One example is his involvement with the International Olympic Committee, which in 2011 revised its policy on athletes who identify as female but who have male sex organs or produce high levels of testosterone.

The issue came to the fore in 2009 after 18-year-old South African runner Caster Semenya, who identifies as female, was subjected to humiliating sex testing before being allowed to continue competing in the women's category.

To head off future problems, the medical advisory board, under Vilain's leadership, drew

a bright line for the 2012 Olympics. People with testosterone levels above 10 nanomoles per litre of blood could not participate in women's events, no matter how they identify. Exceptions are made only if the athletes can prove that they are resistant to the effects of testosterone.

Many activists and ethicists are furious about the policy. "It bears noting that athletes never begin on a fair playing field; if they were not exceptional in one regard or another, they would not have made it to a prestigious international athletic stage," wrote bioethicist Katrina Karkazis from Stanford University in California in a 2012 article<sup>8</sup> lambasting the policy.

Even Vilain struggles to defend it on scientific grounds. Although women with DSDs that result in high testosterone levels are over-represented among Olympians, the hormone does not seem to directly impact their performance. "It is very imperfect," he admits. "But if we don't have a dividing line, then there is no point in segregating sexes in sports." (The policy has been temporarily suspended and is under review.)

Some of Vilain's detractors question how he can support a somewhat arbitrary call in this situation while requiring more evidence to condemn infant surgery. But sport, he argues, depends on rules and policies, whereas medicine relies on best-practice guidelines — and that is what he hopes to develop through research.

He and his collaborators plan to continue the longitudinal study. The team has recruited a bioethicist, John Lantos of Children's Mercy Hospital in Kansas City, to replace Dreger, and it still has some patient advocates involved. Vilain says that he is trying not to antagonize anyone — the next iteration will include research on more questions that the participants say are priorities, such as how to preserve fertility for people with DSDs and identifying cancer risks.

Yet Vilain's experiences with patient advocates have hardened him somewhat. "I call the ones who work with us advocates; those against us activists," he says. He remains driven by questions about sex, even if it kicks up dust. "We're trying to listen to the community, but by the same token we're committed to producing data and evidence." ■

Sara Reardon writes for *Nature* from Washington DC.

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