

# QUANTUM SEX: INTERSEX AND THE MOLECULAR DECONSTRUCTION OF SEX

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*I*ntersex” emerged in the 1990s, a seemingly novel phenomenon with tremendous potential in terms of cultural politics and gender theory. These congenital conditions of atypical genital and gonadal development are at the intersection of sexual biology, social gender determination, and personal identity. As such, intersex conditions challenge traditional medical and cultural principles of sex and gender. American cultural consciousness of intersex conditions arose at the nexus of several events in the 1990s: the rise of intersex activism, the rediscovery of the “John/Joan” case, and the appropriation of intersex in gender studies circles. Cheryl Chase started the Intersex Society of North America (ISNA) in 1993 as an informal support group for adults with intersex conditions.<sup>1</sup> ISNA grew rapidly into a highly vocal and increasingly successful lobbying group that made the American public more aware of intersex individuals and pressed the medical profession to reevaluate the treatment of patients with intersex conditions or what some have recently renamed disorders of sex development (DSDs).<sup>2</sup> In 2008, ISNA was dissolved, and many of those involved with it, including Cheryl Chase (under the name Bo Laurent), shifted the efforts to a new organization, the Accord Alliance, that is focused on DSD-related health care issues.

The popular media first jumped on the subject because of David Reimer, who had been discussed since the 1960s under the pseudonym John/Joan. The journalist John Colapinto described Reimer’s life in a poignant biography/exposé after Reimer had been tracked down by the biologist Milton Diamond and Reimer’s former psychiatrist, H. Keith Sigmundson.<sup>3</sup> Other journalists almost gleefully used the case to assault the psychologist John Money’s theory of gender plas-

GLQ 15:2

DOI 10.1215/10642684-2008-138

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ticity and more fundamentally the concept of gender itself that Money had elaborated in the 1950s.<sup>4</sup> In the popular media the revised moral of the Reimer case was that gender identity is hardwired in the brain in utero, and Money's attempts to tinker with that neuropsychology were misguided if not frankly abusive.<sup>5</sup> By extension some journalists argued that gender studies and all studies relying on social constructionist theory were equally deluded and dangerous: "[Gender] theory rejects the conventional notion of male and female in favor of the ambiguous concept of 'gender.' Its advocates' motto can be described as 'anatomy is not destiny.' . . . The idea that gender is in great part socially determined led doctors to perform the boy's second mutilation [orchietomy]. It has in the intervening years flowered into a reigning dogma in such academic twilight zones as Gender Studies and its cousins."<sup>6</sup> Academic analysts in gender studies, on the other hand, utilized intersexes to further the social constructionist case. Anne Fausto-Sterling early on argued that there are not two sexes, but five.<sup>7</sup> Suzanne J. Kessler argued that gender is not dichotomized but variable and that intersexes will teach us to eliminate the category of gender altogether.<sup>8</sup> Judith Butler erected a straw man argument against the biological determinants of sex by misrepresenting Diamond as a simplistic Y chromosome determinist who supposedly argues that any infant with a Y chromosome should be assigned or reassigned male.<sup>9</sup>

Here I would like to get beyond these Manichaeian debates to argue for an analytics of gender and sexuality that takes the social and the biological seriously by acknowledging the complexity and depth of both influences. The current molecular biology of sex determination is particularly amenable to this kind of analysis, as is contemporary molecular genetics in general. The Mendelian one gene—one trait model has been largely replaced by discussions of oligogenetic and polygenetic traits: a few or many genes conferring small statistical odds for different traits under particular environmental and developmental circumstances. This is particularly true for complex traits.<sup>10</sup> However, this is not the molecular genetics presented in the popular press. A case in point is a 2007 *New York Times* article titled "Pas de Deux of Sexuality Is Written in the Genes."<sup>11</sup> In it Nicholas Wade—by arguing against Butler—tries to explain that "human sexual behavior is not a free-form performance, biologists are finding, but is guided at every turn by genetic programs." According to Wade this all begins in the womb at the moment of sex determination: "In the womb, the body of a developing fetus is female by default and becomes male if the male-determining gene known as SRY is present. This dominant gene, the Y chromosome's proudest and almost only possession, sidetracks the reproductive tissue from its ovarian fate and switches it into becoming testes. Hormones from the testes, chiefly testosterone,

mold the body into male form.” Despite the sexist, anthropomorphizing language of “dominance,” “Y-chromosomal pride,” and ovarian fatalism (to which I will return), this encapsulation of sex determination presents a significant leap forward from simple chromosomal sex determination—the idea that XX chromosomes determine female sex, while XY makes a male. Wade’s explanation, however, is dated and only accords with understandings of sex determination until 1990. The molecular biology of sex determination has become far more complex in the intervening years. For intersex people this molecular complexity is a matter of health as well as sex. Such biological and genetic complexity requires an ever more microscopic—actually molecular—level of understanding of sex in intersex people, and most likely for an ever-increasing number of people with undiagnosed intersex conditions or unexplained hypofertility.

Such complexity also requires a specific and comprehensive understanding, and for that I have to get into some genetic details. As I shortly demonstrate, intersex conditions are extremely diverse (see table 1), so I use the details of one person’s story and intersex biology as the starting point for a broader survey of two decades of sex research. In tracing a path from the chromosomal to the molecular genetics of sex, I point out how this research has shaken off two millennia of Aristotelian sexism to arrive at an interactionist model of genetic sex modifiers that destabilize a binary model of sex in favor of a polymorphic and multifactorial model, which I call quantum sex.

### **Helen and *WT1***

I first met Helen for a psychiatric consultation when she was seventeen. She was an energetic girl who dressed in athletic clothes and described herself as very popular. Although she had graduated from high school, she had had a rocky academic experience because of attentional problems and defiance toward teachers. Helen and her mother concurred that Helen had always been a tomboy with an explosive temper. She also had a complex medical history, of which she had been only partly aware as a child. At age three-and-a-half her kidneys failed, and within a year she required a cadaveric kidney transplant. As a teenager she was placed on “female” hormones (premarin and provera), in addition to the immunosuppressant medications required to sustain her transplant.

It was only at fifteen that she learned of her underlying diagnosis. Unfortunately her mother had revealed this during a fight after discovering love letters from a girl to Helen. Maybe she liked girls, mom blurted out, because she had been born a boy! Soon after this Helen learned that she had been diagnosed in

Table 1. Estimated Frequency of Intersex-Related Diagnoses

Cause	Estimated frequency/ 100 live births
Non-XX and non-XY (except Turner and Klinefelter)	0.0639
Turner (X)	0.0369
Klinefelter (XXY)	0.0922
Subtotal for chromosomal difference	0.193
Androgen insensitivity syndrome	0.00760
Partial androgen insensitivity syndrome	0.000760
Classical congenital adrenal hyperplasia (CAH)	0.00770
Late onset CAH	1.5
Subtotal for known hormonal causes	1.516
Vaginal agenesis	0.0169
True hermaphrodites (ovotestes)	0.0012
Idiopathic	0.0009
Total (aside from hypospadias)	1.728
Hypospadias	1.87 ± 1.105

Source: Adapted from Melanie Blackless et al., "How Sexually Dimorphic Are We? Review and Synthesis," *American Journal of Human Biology* 12 (2000): 159, 160.

Note: These figures present an upper-limit estimate of the prevalence of all intersex diagnoses organized into three main classes of disorders. Hypospadias is an extremely common male birth defect; however, third-degree hypospadias with genital ambiguity is rare. Leonard Sax has pointed out that these figures overrepresent the frequency of intersex by including the full prevalence of diagnoses (such as congenital adrenal hyperplasia), which only present with genital ambiguity in severe cases. Sax's more conservative estimate of the prevalence of genital ambiguity and "sex reversal" (discordant sex chromosomes and genitalia) is 0.018 percent of live births ("How Common Is Intersex? A Response to Anne Fausto-Sterling," *Journal of Sex Research* 39 [2002]: 174–78).

infancy with Denys-Drash syndrome (DDS). She had a 46XY chromosomal karyotype, and in her first year of life had undergone a laparotomy during which dysfunctional testes were removed to prevent later testicular cancer. She was found to have a vagina but no uterus. Two years later she underwent so-called corrective reduction of her clitoris.

DDS is characterized by a 46XY karyotype with ambiguous genitalia, but in 40 percent of cases there are completely unremarkable female external geni-

talia.<sup>12</sup> Renal disease usually begins in the first year of life, and there is a high frequency of Wilms' tumor of the kidney. In 1990 Wilms' tumor was found to be associated with mutations in a gene that was named *WT1* (Wilms' tumor-1).<sup>13</sup> The protein product of *WT1* was found to be a group of DNA-binding proteins that act as transcriptional activators or repressors (they turn particular genes on or off) depending on cellular environment and other genetic factors.<sup>14</sup> Given that a mutation in *WT1* was associated with tumors, it was presumed to be a tumor-suppressor gene. Since 1991, however, genetic studies of DDS patients have found that DDS is also associated with *WT1* point mutations (of a single DNA base pair).<sup>15</sup> So *WT1* is a gene not only associated with testicular cancer but also essential for testicular development and male sex determination. Thirty-four different critical mutations in *WT1* have been found to be associated with female genital development in XY individuals.<sup>16</sup> But the curious thing is that *WT1* is not on the so-called sex chromosomes, X and Y. *WT1* is on the short arm of chromosome 11 (11p13), one of the autosomes (chromosomes other than X or Y). To understand how researchers arrived at this conundrum of sex-determining genes on non-sex-chromosomes we need to review a century of sex determination research and its underlying sexist hypotheses.

### From Bisexual Gonads to *SRY*

The biological difference between the sexes versus their transmutability has been debated since antiquity.<sup>17</sup> Comparative anatomists in the mid-nineteenth century had discovered that, at very early stages of mammalian embryonic development, immature gonadal and genital tissues look identical in males and females. Victorian sexologists would therefore write of the "bisexuality" of the mammalian embryo.<sup>18</sup> At this developmental stage the genital and gonadal tissue is therefore described (even in current biological literature) as "indifferent." The primordial genital tissue can develop into labia majora or fuse as a scrotum, while the phallus can take on clitoral or penile appearance. Internally primordial gonadal tissue develops into ovarian or testicular tissue (and extremely rarely a mixture of these). The embryo is also "bisexual" in terms of the genital ductal system; however, these are *parallel* systems rather than derived from the same tissue. In other words, *both* the Müllerian ducts and the Wolffian ducts are present at an early stage in development, with subsequent degeneration of one of the two ductal systems.<sup>19</sup> It is only by the second month postconception in humans that there usually is differentiation into typical female or male sexual anatomy.<sup>20</sup>

What makes most embryos develop in one direction or the other? Fin de siècle biologists widely believed that environmental factors (such as temperature and nutrition) determined sex.<sup>21</sup> The first suggestion of a connection between chromosomes and sex was published by H. Henking in 1891.<sup>22</sup> In the fire bug, *Pyrrhocorts apterus*, Henking noted that the female had twenty-four chromosomes, while the male seemed to have twenty-three. Uncertain whether this solitary structure (which he called a “nucleolus”) was an additional chromosome, he labeled it *X* in his drawing (leading to the term *X chromosome*). He noted that *P. apterus* spermatozoa came in two varieties: those with and those without the “nucleolus.” Following on Henking’s discovery, Clarence E. McClung made the bold hypothesis that this “nucleolus” was not just an effect of sex determination but the cause of it. He proposed that the “nucleolus” is a sex-determining “accessory chromosome” carried on the “motile” spermatozoa — not the “passive” ova — and “is the bearer of those qualities which pertain to the male organism.”<sup>23</sup>

Gregor Mendel’s pioneering studies from the 1860s of trait inheritance in peas were only rediscovered in 1900. Sex determination by chromosomes — following Mendelian inheritance patterns — was demonstrated soon thereafter by Nettie Maria Stevens and Edmund Beecher Wilson. In 1905 Stevens described the small and large sex chromosomes in the mealworm, which has an XX/XY sex chromosome system (as in mammals).<sup>24</sup> The same year Wilson described how in the squash bug, *Anasa tristis*, the female has twenty-two chromosomes, while the male has twenty-one (a 22,X/21,0 sex chromosome system).<sup>25</sup> Wilson’s discovery not only challenged but inverted McClung’s theory that males bear the sex-determining chromosomal factor. In the squash bug it is the female that has the supplemental chromosome. After Stevens’s and Wilson’s work, chromosomal sex determination became increasingly widely accepted among biologists, and further studies in different species demonstrated that there are a variety of sex chromosome systems among animals.<sup>26</sup>

If one pair of chromosomes differs between male and female mammals, it was a logical hypothesis that these “sex chromosomes” determined sex because they contained sex-determining genes. Since mammalian males (XY) and females (XX) both have at least one X chromosome, the Y chromosome seemed to be a likely site for a male-determining gene. The French physiologist Alfred Jost discovered that by transplanting testes into rabbit embryos (whether XX or XY) he could force male sexual development.<sup>27</sup> Conversely, removal of gonadal tissue before its differentiation into testes would lead to female differentiation of the remaining reproductive system. Jost therefore proposed that there was a testis-determining factor (TDF) that first triggered the differentiation of the bipotential gonad into

a testicle. After this, the testicle produced other hormones that would direct the further differentiation of the reproductive system in a male direction. Thus Jost conceptually divided the embryology of sex into two stages: “sex determination” (inducing testis formation) and “sex differentiation” (subsequent differentiation of the internal and external reproductive system).<sup>28</sup>

Jost’s hypothesis follows a neo-Aristotelian philosophy of sex: males require an *active* process to develop (the TDF), whereas female development occurs *passively* and by default (because of the maternal hormonal milieu). Aristotle in *Generation of Animals* presented the two sexes as being of distinct principles: the male contains the “principle of movement and generation,” while the female contains the principle of “matter.”<sup>29</sup> The female semen (menstrual fluid) contributes the *material* of the embryo, which is given *form* by the male semen because it alone possesses the principle of soul (ψυχή). For Aristotle, the female is “as it were a mutilated male” (737a25). It is the male who contributes the active component that leads to the greater vital heat necessary for the formation of a male fetus. If the father is healthy and not too young or too old he will produce stronger, more active male semen that is more likely to prevail over the female material and thereby generate male offspring (776b30).<sup>30</sup> McClung’s accessory chromosome model similarly had a neo-Aristotelian foundation: male sex determination needs supplemental active genetic intervention, while a female outcome is the result of a genetic deficit. Jost’s developmental model was explicitly testocentric: some active supplemental genetic influence is needed to trigger testis formation, whereas the ovary is relegated to being a default organ requiring no particular genetic machinery worthy of investigation. This is still the philosophical underpinning of Wade’s summary of sex determination in his 2007 *New York Times* article.

Until the 1990s geneticists searched the Y chromosome for a testis-determining gene to the neglect of ovarian development. The science historian Sarah S. Richardson highlights how women biologists such as Eva M. Eicher, Linda L. Washburn, and Fausto-Sterling in the mid-1980s highlighted the sexism underlying the research agenda of searching for a testis-determining gene on the Y chromosome—or what I call the testocentric hypothesis.<sup>31</sup> After many false leads, molecular biologists in 1990 identified a testis-determining gene on the Y chromosome and named it *SRY* (sex-determining region of the Y).<sup>32</sup> It was identified thanks to rare intersex individuals who are XX males or XY females because *SRY* crossed over from the Y to the X chromosome during spermatogenesis.

Subsequent *Sry* transfection experiments in mice confirmed that it was a testis-determining gene, since it could induce testicle formation in XX mice. Like *WT1* in humans, the *Sry* gene in mice was found to code for a protein (labeled

SRY) that binds DNA, causing it to bend at a specific angle that may help facilitate transcription (from the DNA code to RNA and eventually a protein).<sup>33</sup> The gene is active in the developing mouse gonadal ridge during a short critical period in development when the indifferent gonad takes the step toward developing as a testis. It is still not understood, however, what exactly the *SRY* protein product *does* to induce testicular development.

The discovery of *SRY*—the “dominant gene” and “the Y chromosome’s proudest possession,” as Wade put it—did not finally solve the mystery of sex. Instead, actual intersex individuals in all their diversity confounded the elegant simplicity of the testocentric model—initiating its rapid deconstruction. With *SRY* identified and genetic testing significantly simpler and cheaper in the 1990s, subsequent genetic studies of intersexed people found that there are 46XX individuals with testes who do *not* possess the *SRY* gene, suggesting that some other gene or genes can induce testis determination in the absence of *SRY*. Geneticists also discovered 46XY individuals with ovaries who have duplication of an X chromosome gene labeled *DAX-1*, which if present in a double dose can override *SRY*-stimulated testis development. Subsequent research has suggested that *WT1* increased expression of the *SRY* gene.<sup>34</sup> Researchers hypothesize that *SRY* is involved in a double inhibition pathway—repressing a subsequent factor that represses maleness.<sup>35</sup>

Rapid advances in the genetics of sex determination have completely trashed the 1950s notion that the human Y chromosome alone determines male sex. At this point genes from chromosomes 9 (*SF-1*), 11 (*WT-1*), 17 (*SOX-9*), 19 (*MIS*), and the X chromosome (*DAX-1*) in addition to *SRY* on the Y chromosome (or sometimes on the X) are essential for the usual development of testes and male internal and external genitalia (see table 2). Further, these genes’ proteins have multiple sites of action beyond the gonads. *SRY*, for example, appears to be consistently expressed in mammals around the time of testis differentiation, but in different mammal species is expressed in other tissues at other times. Its function is not limited to testis determination; therefore its name, like that of so many genes—such as Wilms’ tumor-1—is a misnomer as well as a historical artifact just like the “sex chromosomes” and the “sex hormones.”<sup>36</sup> What is more, at every step of these genes’ action there are critical points where the effects of environment, particularly neighboring tissue and gene expression, modulates or thwarts their usual functions. Most dramatically, many reptiles and some fish lack sex chromosomes entirely, and sex is determined by environmental factors such as temperature.<sup>37</sup>

Table 2. Genes Involved in Mammalian Sex Determination

Gene	Chromosomal localization	Putative function	Phenotype of mutations
<i>SF-1</i>	9q33	Transcription factor	XY gonadal dysgenesis and adrenal insufficiency
<i>WT-1</i>	11p13	Transcription factor	Denys-Drash and Frasier syndromes
<i>SRY</i>	Yp11.3	Transcription factor	Feminized XY and gonadal dysgenesis
<i>DAX1</i>	Xp21.3	Transcription factor	Duplication: XY gonadal dysgenesis Mutation: adrenal hypoplasia congenita
<i>SOX9</i>	17q24	Transcription factor	Duplication: masculinized XX Mutation: campomelic dysplasia with XY gonadal dysgenesis
<i>M33</i>	17q25	Transcription factor	Feminized XY
<i>Fgf9</i>	13q11–13	Signaling molecule	Feminized XY and gonadal dysgenesis
<i>DMRT1</i>	9p24.3	Transcription factor	Deletion: feminized XY, gonadal dysgenesis, microcephaly, mental retardation
<i>AMH</i>	19p13	Signaling molecule	XY persistent Müllerian duct derivatives
<i>DHH</i>	12q13.1	Signaling molecule	Mutation: XY gonadal dysgenesis with neuropathy
<i>ATRX</i>	Xq13	Helicase	Feminized XY, mental retardation, $\alpha$ -thalassemia
<i>WNT-4</i>	1p35	Signaling molecule	Duplication: XY gonadal dysgenesis Mutation: masculinized XX
<i>Gdf9</i>	5p11	Signaling molecule	Ovarian follicular failure
<i>FOXL2</i>	3q23	Transcription factor	Premature ovarian failure and eyelid defects

Source: Adapted from Corinne Cotinot et al., "Molecular Genetics of Sex Determination," *Seminars in Reproductive Medicine* 20 (2002): 158; Eric Vilain, "Genetics of Intersexuality," *Journal of Gay and Lesbian Psychotherapy* 10 (2006): 13; and Berenice B. Mendonca, Soharía Domenice, Ivo J. P. Arnhold, and Elaine M. F. Costa, "46,XY Disorders of Sex Development," *Clinical Endocrinology*, postprint, September 22, 2008, [www3.interscience.wiley.com/cgi-bin/fulltext/121414874/PDFSTART](http://www3.interscience.wiley.com/cgi-bin/fulltext/121414874/PDFSTART).

Throughout the 1990s, then, Jost's testocentric model quickly unraveled under mounting evidence of the enormous complexity of mammalian sex determination, prompting the Australian molecular biologist Jennifer A. Marshall Graves to publish an article titled "Human Y Chromosome, Sex Determination, and Spermatogenesis — a Feminist View."<sup>38</sup> Although Richardson has argued that Graves as a scientific insider "normalized" the earlier feminist critique of the field, Graves never cites Fausto-Sterling's work or any social constructionist studies.<sup>39</sup> She apparently was less driven by feminist science studies than the internal collapse of what she humorously called the "macho" Y model under the growing weight of molecular biological findings. Graves hypothesizes instead that the Y chromosome is a "wimpy" chromosome, having lost many genes throughout mammalian evolution, and at the rate it is going will eventually vanish entirely in ten to a hundred million years. Sex determination will instead be taken over by the autosomal genes, as is now the case in mole voles (in which both sexes have a single X chromosome [in *Ellobius lutescens*] or XX [in *E. tancrei*]).

As the genetics of testicular development has become ever more complex in the past seventeen years, researchers have discovered it is intricately interwoven with the long-neglected genetics of ovarian development. A recent review article on ovarian development research opens by challenging the neo-Aristotelian perspective that has dominated the field: "Increasing evidence indicates that organogenesis of the ovary is not a passive process arising by default in the absence of the testis pathway."<sup>40</sup> Not surprisingly, ovarian development is proving to be as complex and polygenetic, with some genes promoting ovarian development and others suppressing testicular development. Finally, the discovery of XX individuals with testicular structures despite the absence of *SRY* has led one researcher to suggest that perhaps ovarian development is the active process and testicular development the passive default pathway — completely inverting the testocentric hypothesis.<sup>41</sup>

### Gender and the Brain

The preceding discussion does not even begin to address the issues of gender identity and sexuality, which may also have some congenital, organic, and neurological foundations. Recent work in molecular genetics may shed new and controversial light on neuroanatomical sex differences. Phoebe Dewing and her colleagues in the lab of Eric Vilain, using microarray technology, have detected fifty-one out of twelve thousand genes active in the brain that are expressed at significantly different levels in male versus female mice at 10.5 days of embryogenesis (days

postcoitum).<sup>42</sup> Since the nineteenth century, neuroanatomists have noted gross differences between male and female brains that were largely related to average differences in body size between men and women. But sex-specific differences in discrete brain regions have led to all sorts of speculation about their functional impact on cognition and behavior. The neuroscientist Simon LeVay made front-page news in 1991 with a very preliminary finding that (on average) there is a size difference in a region of the hypothalamus between homosexual and heterosexual men.<sup>43</sup> Whether associated with differences in gender or sexual orientation, these neuroanatomical differences were assumed by LeVay to be the result of in utero hormonal differences induced by the fetal gonads or the maternal hormonal milieu.<sup>44</sup>

What is striking, however, about Dewing's current research is that the differential gene expression was evident *before* the embryonic gonads had formed and could have produced androgens or estrogens. Contrary to LeVay's assumption of hormonal influences, Dewing's work argues that there are *genetically* induced sex differences in brain development. Again, the functional significance of these findings, if replicated, is up for speculation. Vilain, however, believes this murine research suggests genetic mechanisms of gender identity in the human brain with potential clinical value in assigning gender to neonates with ambiguous genitalia.<sup>45</sup> This line of research also potentially indicates a genetic basis for transsexualism and more broadly gender atypical behavior, if indeed there are genetic markers of neurological sex difference that more closely predict gender identity than even the sex chromosome karyotype. Whereas biologists (such as LeVay) are willing to conflate gender atypicality (the Victorian notion of "sexual inversion") and homosexuality, this research points to new genetic approaches to studying sexual orientation. Differential gene expression in *adult* male versus female brains will be another area of research used to explain sex differences in behavior: Dewing and her colleagues have presented data showing that *Sry* expression in rodents has an influence on the functioning of a specific, sexually dimorphic area of the rodent brain that affects movement.<sup>46</sup>

This neurogenetic research into sex differences is in its infancy and undoubtedly still fired by a conceptual ambitiousness inspired by limited data. However, if genital sex differentiation is any indicator, the biology of gender identity will most likely be even more complex in its molecular and hormonal mechanisms. Therefore only the most distorted and simplistic reading of the contemporary molecular biology of sex determination would suggest that it leads to a dichotomization of sex or gender. On the contrary, I find that this research deconstructs all prior Western scientific representations of sex, indicating instead the tremendous diversity of even the anatomical manifestations of sex. Extrapolating

from this we would have to imagine that the diverse expressions of gender behavior and identity will prove even more complex and multideterminate in their biology, and regularly resist and challenge one gene–one trait models.

### Microarray Gene Testing and Quantum Sex

In closing, let me return to Helen, who at just seventeen had to contend with huge anatomical, medical, familial, and social challenges. Although 46XY, her genital appearance was female, and there was never any question of gender reassignment simply to follow the dictates of her Y chromosome. Her kidney failure and transplant were one of the unfortunate defining features of DDS. The clitoral reduction, however, was medically unnecessary, and this type of “corrective” surgery has come under intense criticism thanks to ISNA activism.<sup>47</sup> The secrecy surrounding her diagnosis and treatment, while intended to protect her from the shock of her condition and any gender ambiguity, is probably misguided. She needs to understand her medical condition because she needs to remain under close medical attention her whole life, if only because of the kidney transplant. Correspondingly, over the past decade ISNA’s position evolved toward greater collaboration with medical specialists to improve evaluation, education, and care of intersex patients, rather than a radical identity politics of demolishing the binary sex system in favor of a gender-free or gender-rainbow society.<sup>48</sup> This partnership with health care professionals is even more clearly enunciated as the mission of the new Accord Alliance that replaced ISNA in March 2008.

I would predict, however, that ISNA’s treatment recommendations are likely to have increasing utility precisely as the binary sex system becomes ever more ragged at the edges. I am not suggesting that sex is not primarily bimodal—with two curves corresponding to two typical functional outcomes, male and female. Indeed, intersex conditions largely reinforce this, because in most cases where there are chromosomal or genetic anomalies the result is infertility or reduced fertility. The swiftly expanding research on the molecular genetics of gonadal development and neurological sex differences is certain to increase the overlapping tails of those male and female curves. This will particularly be true with DNA microarray technology.

Over the last decade of intense research fueled by the \$3 billion Human Genome Project, the estimated total gene count for the human genome has shrunk to between twenty thousand and twenty-five thousand genes. Meanwhile, microarray testing has automated genetic testing such that over a half million probes of different genetic variations can be examined on a chip the size of a postage stamp

for \$250.<sup>49</sup> Accordingly whole human genome testing is now a reality and will become ever more inexpensive.<sup>50</sup> It will become increasingly feasible to identify an individual's genetic variations or mutations of all genes or select genes. For example, prenatal genetic screening could be done for all thirty-five variants of the *WTL* gene as well as variants of all the other sex-determining genes known at the time, for an up-to-date sex genotype. Instead of simple sex chromosome data (usually XX or XY), parents would be presented with data on a dozen or, in the future, dozens of sex-related genes.

Leaping from this genotyping to an understanding of an individual's *phenotype*, however, will involve a complex statistical calculus. For example, there may be thirty-five variations of the *WTL* gene (*WTL* genotypes), each of which conveys certain statistical odds of particular anatomical and physiological outcomes (phenotypes). The specific phenotype—whether at birth or later in life—will also depend on the genotype of other genes (such as *SRY* and *DAX-1*) and their particular odds of producing certain phenotypes depending on the interaction of genes and tissues in embryogenesis or interactions with environmental factors later on in life. Sex determination will no longer be the simple matter of identifying a penis on ultrasound or XX/XY sex chromosome identification from an amniocentesis.

Molecular genetics is likely to require a shift from binary sex to quantum sex, with a dozen or more genes each conferring a small percentage likelihood of male or female sex that is still further dependent on micro- and macro-environmental interactions. As David Crews and colleagues point out: “Genes are not expressed in isolation any more than social behavior has meaning outside of society. Both are in dynamic flux with the immediate environment that the gene/individual finds itself, which in turn establishes the timing, pattern, and conditions of expression.”<sup>51</sup> Some biologists and science critics have long pointed out that nature and nurture are intimately intertwined. In the 1940s and 1950s Barbara McClintock had been studying gene transposition as a mechanism by which the environment could regulate genes in maize. Evelyn Fox Keller's biography of McClintock highlighted how she had to develop a new methodology and language to elaborate a dynamic model of interaction between the environment and the organism.<sup>52</sup> While it took several decades for McClintock's work to be rediscovered and accepted, research on sex determination afforded by intersex cases has prompted a dramatic shift within a decade. The hypothesis of a single testis-determining gene on the Y chromosome has quickly given way to a multigenetic network of gene regulation with time- and environment-sensitive factors.

The form of sex that emerges out of this quantum cloud of biological and environmental effects is at once culturally defined and personally discovered.

Helen's experience of her sex, gender, and sexuality is intimately tied to her sense of her body—to what is evident on the surface, to what she understands to be her internal anatomy, to her lost genital and gonadal flesh, and to her genetic makeup. At seventeen she was probably not conscious of the historical and cultural constructions of gender, intersexes, and sexuality that have influenced what happened to her body, yet she will have to construct for herself a new experience of her body that allows for sexual intimacy, erotic pleasure, and a fulfilling relationship with women, men, or both. The new molecular genetics of sex is likely to pose similar ontological and existential challenges to an increasing number of people with medical issues less life threatening than Helen's. The new DSD terminology tends to narrow the sphere of intersex to individuals with clear pathology of the reproductive system. This is a practical taxonomic move for focusing on the problem of early genital corrective surgery. I would predict, however, that the complex new molecular genetics of sex—along with widespread genetic testing—will widen the sphere or, at least, further blur the boundaries of what is intersex. Thus the medical and sociopolitical challenge of intersexuality will hopefully prompt a broader and more complex understanding of sex/gender/sexuality as a biological, psychological, and cultural phenomenon that is rich, diverse, and indefinitely complex, resistant to all simplistic reductionism, whether biological or discursive.

### Notes

1. Cheryl Chase, letter to the editor, *Sciences*, July–August 1993, 3.
2. A new nomenclature using the term *DSD* was hammered out by a consensus group of pediatric endocrinologists, urologists, and geneticists, with much support from ISNA; see Peter A. Lee et al., “Summary of Consensus Statement on Intersex Disorders and Their Management,” *Pediatrics* 118 (2006): 753–57; Alice Dreger et al., “Changing the Nomenclature/Taxonomy for Intersex: A Scientific and Clinical Rationale,” *Journal of Pediatric Endocrinology* 18 (2005): 729–33; Eric Vilain et al., “We Used to Call Them Hermaphrodites,” *Genetics in Medicine* 9 (2007): 65–66. This change represents ISNA's decisive move to reconstruct intersex as a medical matter and not one of cultural identity politics. In this essay I continue to use *intersex* because of its familiarity and to highlight its cultural messiness rather than sanitize it with a medicalizing acronym. The DSD acronym is predictably controversial among some intersex activists committed to a radical depathologization of intersex and a critique of the “dogmatic fundamentalism inherent in the current binary construct of sex and gender” (Organisation Intersex International, “DSD—Is There Really a Consensus?” [www.intersexualite.org/Disorders\\_of\\_Sex\\_Development.html](http://www.intersexualite.org/Disorders_of_Sex_Development.html) [accessed July 29, 2008]). The intersex activist Emi Koyama offers a pragmatic acceptance of the

- DSD term in the context of disability studies and a politics of depathologizing pathology itself (“From ‘Intersex’ to ‘DSD’: Toward a Queer Disability Politics of Gender” [2006], [www.intersexinitiative.org/articles/intersectods.html](http://www.intersexinitiative.org/articles/intersectods.html)).
3. John Colapinto, *As Nature Made Him: The Boy Who Was Raised as a Girl* (New York: HarperCollins, 2000); Milton Diamond and H. Keith Sigmundson, “Sex Reassignment at Birth: Long-Term Review and Clinical Implications,” *Archives of Pediatric and Adolescent Medicine* 151 (1997): 298–304.
  4. Bernice L. Hausman, *Changing Sex: Transsexualism, Technology, and the Idea of Gender* (Durham, NC: Duke University Press, 1995), 95.
  5. Natalie Angier, “Sexual Identity Not Pliable After All, Report Says,” *New York Times*, March 14, 1997.
  6. “Anatomy Is Destiny,” *New York Post*, March 17, 1997.
  7. Anne Fausto-Sterling, “How Many Sexes Are There?” *New York Times*, March 12, 1993.
  8. Suzanne J. Kessler, *Lessons from the Intersexed* (New Brunswick: Rutgers University Press, 1998), 132.
  9. Judith Butler, “Doing Justice to Someone: Sex Reassignment and Allegories of Transsexuality,” *GLQ* 7 (2001): 621–36. Milton Diamond rebuts her in “Biased-Interaction Theory of Psychosexual Development: ‘How Does One Know If One Is Male or Female?’” *Sex Roles* 55 (2006): 589–600.
  10. C. E. M. van Beijsterveldt, James J. Hudziak, and Dorret I. Boomsma, “Genetic and Environmental Influences on Cross-Gender Behavior and Relation to Behavior Problems: A Study of Dutch Twins at Ages 7 and 10 Years,” *Archives of Sexual Behavior* 35 (2006): 647–58.
  11. Nicholas Wade, “Pas de Deux of Sexuality Is Written in the Genes,” *New York Times*, April 10, 2007.
  12. S. J. McTaggart et al. “Clinical Spectrum of Denys-Drash and Frasier Syndrome,” *Pediatric Nephrology* 16 (2001): 335–39.
  13. A note on abbreviation and typesetting conventions in molecular genetics: abbreviations of gene names are italicized. The protein for which the gene codes is designated in nonitalics. For example, the *WT1* gene codes for WT1 protein. Human genes are abbreviated in capitals, while in other animals only the first letter of the gene name is capitalized—for example, *Wt1* in humans, *Wtl* in mice.
  14. Anwar Hossain and Grady F. Saunders, “The Human Sex-Determining Gene *SRY* Is a Direct Target of *WT1*,” *Journal of Biological Chemistry* 276 (2001): 16817–23; Jürgen Klattig et al., “Wilms’ Tumor Protein *Wt1* Is an Activator of the Anti-Müllerian Hormone Receptor Gene *Amhr2*,” *Molecular and Cellular Biology* 27 (2007): 4355–64.
  15. A similar condition, Frasier syndrome (characterized by 46XY karyotype, normal female genitalia, streak gonads, and later renal disease but no tumor), was found to

- be associated with a different set of mutations in *WT1* (A. Koziell et al., “Frasier Syndrome: Part of the Denys-Drash Continuum or Simply a *WT1* Gene-Associated Disorder of Intersex and Nephropathy?” *Clinical Endocrinology* 52 [2000]: 519–24).
16. R. F. Mueller, “The Denys-Drash Syndrome,” *Journal of Medical Genetics* 31 (1994): 471–77.
  17. Thomas Laqueur, *Making Sex: Body and Gender from the Greeks to Freud* (Cambridge, MA: Harvard University Press, 1990).
  18. James Kiernan, “Sexual Perversion,” *Detroit Lancet* 7 (1884): 481–84.
  19. The paired Müllerian (or paramesonephric) ducts develop into the female internal reproductive organs—fallopian tubes, uterus, cervix, and upper two-thirds of the vagina. The lower third of the vagina develops from the invagination of the urogenital sinus on the external surface of the groin. Failure of the lower part of the paired ducts to fuse leads to a bicornuate (two-horned) uterus. In males the Müllerian ducts usually degenerate because of testicular secretion of Anti-Müllerian hormone (AMH), leaving behind an appendix testis on each side. The AMH gene is at locus 19p13.3—also not on the sex chromosomes. The paired Wolffian (or mesonephric) ducts usually develop with the stimulation of testosterone into the male reproductive tract connecting the testes to the exterior—rete testis, epididymis, vas deferens, seminal vesicle, and central zone of the prostate. The peripheral and transitional zones of the prostate develop from the urogenital sinus. Usually in females the Wolffian duct degenerates, leaving behind a remnant, the Gartner duct.
  20. At thirty-two days postconception in humans the primordial germ cells begin to differentiate. At fifty-five to sixty days anti-Müllerian hormone begins to be secreted and the Müllerian duct begins to regress in males. At nine weeks testosterone is produced in males, and there is masculinization of the urogenital sinus and external genitalia. At ten weeks the Wolffian ducts regress in females.
  21. Stephen G. Brush, “Nettie M. Stevens and the Discovery of Sex Determination by Chromosomes,” *Isis* 69 (1978): 165; Jane Maienschein, “What Determines Sex? A Study of Converging Approaches, 1880–1916,” *Isis* 75 (1984): 456–80.
  22. H. Henking, “Untersuchungen über die ersten Entwicklungsvorgänge in der Eiern der Insekten II: Über Spermatogenese und deren Beziehung zur Eientwicklung bei *Pyrrhocoris apterus*” (“Investigations into the Early Developments of Insect Eggs II: Concerning Spermatogenesis and Its Relationship to Egg Development in *Pyrrhocoris apterus*”) *Zeitschrift wissensch Zoologie* 51 (1891): 685–736.
  23. C. E. McClung, “The Accessory Chromosome—Sex Determinant?” *Biological Bulletin* 3 (1902): 72.
  24. Nettie M. Stevens, *Studies in Spermatogenesis with Especial Reference to the “Accessory Chromosome”* (Washington, DC: Carnegie Institution, 1905).
  25. Edmund B. Wilson, “Studies on Chromosomes I: The Behavior of the Idiochromosomes in *Hemiptera*,” *Journal of Experimental Zoology* 2 (1905): 371–405.

26. Derek Chadwick and Jamie Goode, eds., *The Genetics and Biology of Sex Determination* (New York: Wiley, 2002).
27. Alfred Jost, “Recherches sur la différenciation sexuelle de l’embryon de lapin III: Rôle des gonades foetales dans la différenciation sexuelle somatique” (“Research into the Sexual Differentiation of the Rabbit Embryo III: The Role of Fetal Gonads in Somatic Sexual Differentiation”), *Archives d’Anatomie Microscopique et de Morphologie Expérimentale* 36 (1947): 271–315.
28. Once testes begin to develop they produce Müllerian inhibiting substance, which inhibits the further development of Fallopian tubes and uterus, and the testes secrete testosterone, which stimulates development of male internal genitalia and masculinization of the external genitalia.
29. Aristotle, *Generation of Animals*, trans. A. L. Peck (Cambridge, MA: Harvard University Press, 1942), 716a5.
30. See also Joan Cadden, *Meanings of Sex Difference in the Middle Ages: Medicine, Science, and Culture* (New York: Cambridge University Press, 1993).
31. Sarah S. Richardson, “When Gender Criticism Becomes Standard Scientific Practice: The Case of Sex Determination Genetics,” in *Gendered Innovations in Science and Engineering*, ed. Londa Schiebinger (Stanford: Stanford University Press, 2008), 22–42. Eicher and Washburn in a review of mouse sex determination research pointed out that researchers represent testis determination as an active gene-directed event, while the induction of the ovary is a default passive event. This leads to the complete neglect of genetic research on ovarian tissue development, which they point out must be as active and genetically directed as any tissue development (“Genetic Control of Primary Sex Determination in Mice,” *Annual Review of Genetics* 20 [1986]: 328). Fausto-Sterling in her “Life in the XY Corral” (*Women’s Studies International Forum* 12 [1989]: 319–31) cited Eicher and Washburn in a more pointedly feminist critique of the female passivity ideology underlying David Page’s 1987 identification—which ultimately proved erroneous—of a testis-determining gene.
32. Philippe Berta et al., “Genetic Evidence Equating *SRY* and the Testis-Determining Factor,” *Nature* 348 (1990): 448–50; Ralf J. Jäger et al., “A Human XY Female with a Frame Shift Mutation in the Candidate Testis-Determining Gene *SRY*,” *Nature* 348 (1990): 452–54; Christopher M. Haqq and Patricia K. Donahoe, “Regulation of Sexual Dimorphism in Mammals,” *Physiological Reviews* 78 (1998): 1–33.
33. Nelson B. Phillips et al., “*SRY* and Human Sex Determination: The Basic Tail of the HMG Box Functions as a Kinetic Clamp to Augment DNA Bending,” *Journal of Molecular Biology* 358 (2006): 172–92.
34. Hossain and Saunders, “Human Sex-Determining Gene *SRY*.”
35. Paul D. Waters, Mary C. Wallis, and Jennifer A. Marshall Graves, “Mammalian Sex—Origin and Evolution of the Y Chromosome and *SRY*,” *Seminars in Cell and Developmental Biology* 18 (2007): 389–400.

36. Nelly Oudshoorn, "On the Making of Sex Hormones: Research Materials and the Production of Knowledge," *Social Studies of Science* 20 (1990): 5–33.
37. Waters et al., "Mammalian Sex."
38. Jennifer A. Marshall Graves, "Human Y Chromosome, Sex Determination, and Spermatogenesis—a Feminist View," *Biology of Reproduction* 63 (2000): 667–76.
39. Richardson, "When Gender Criticism Becomes Standard Scientific Practice."
40. Humphrey Hung-Chang Yao, "The Pathway to Femaleness: Current Knowledge on Embryonic Development of the Ovary," *Molecular and Cellular Endocrinology* 230 (2005): 87.
41. Yao, "Pathway to Femaleness," 91.
42. Phoebe Dewing et al., "Sexually Dimorphic Gene Expression in Mouse Brain Precedes Gonadal Differentiation," *Molecular Brain Research* 118 (2003): 82–90.
43. Simon LeVay, "A Difference in Hypothalamic Structure between Heterosexual and Homosexual Men," *Science* 253 (1991): 1034–37.
44. For contrasting accounts, see G. Dörner et al., "Gene- and Environment-Dependent Neuroendocrine Etiogenesis of Homosexuality and Transsexualism," *Experimental and Clinical Endocrinology* 98 (1991): 141–50; and Roger A. Gorski, "Sexual Differentiation of the Endocrine Brain and Its Control," in *Brain Endocrinology*, ed. Marcella Motta (New York: Raven, 1991), 71–104.
45. Carina Dennis, "The Most Important Sexual Organ," *Nature* 427 (2004): 390–92.
46. Phoebe Dewing et al., "Direct Regulation of Adult Brain Function by the Male-Specific Factor SRY," *Current Biology* 16 (2006): 415–20.
47. Cheryl Chase, "Hermaphrodites with Attitude: Mapping the Emergence of Intersex Political Activism," *GLQ* 4 (1998): 189–211.
48. See ISNA's Web site promoting the new DSD terminology and treatment guidelines: [www.dsdguidelines.org](http://www.dsdguidelines.org).
49. This Genome-Wide Human SNP Array 5.0 is produced by Affymetrix: [www.affymetrix.com/products/arrays/specific/genome\\_wide/genome\\_wide\\_snp\\_5.affx](http://www.affymetrix.com/products/arrays/specific/genome_wide/genome_wide_snp_5.affx) (accessed July 29, 2008).
50. In May 2007 the Baylor College of Medicine and gene-testing technology company 454 Life Sciences announced the sequencing of a complete human genome, that of DNA codiscoverer James Watson: [www.454.com/watson](http://www.454.com/watson) (accessed July 29, 2008).
51. David Crews et al., "From Gene Networks Underlying Sex Determination and Gonadal Differentiation to the Development of Neural Networks Regulating Sociosexual Behavior," *Brain Research* 1126 (2006): 109.
52. Evelyn Fox Keller, *A Feeling for the Organism: The Life and Work of Barbara McClintock* (San Francisco: Freeman, 1983).