The Embryology of Gender

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More than 50 years after the appearance of the term “gender” in the clinical setting, we have yet to uncover the mechanisms and factors that lead to gender identity formation. Based on human embryology principles, the scientific reasoning with regard to the sexual differentiation of the body is erroneously applied to gender identity formation. The term “embryology of gender” draws attention to the inherent contradictions of trying to apply biological principles to gender development. It is concluded that the clinical management of gender secures the dyad sex:gender by managing the boundaries of what constitutes the acceptable male and female forms.

KEYWORDS Behavioral neuroendocrinology, embryology, gender identity, intersexuality, sexual anatomy, sex determination, transsexuality

In the early 1980s, an interdisciplinary collaboration between pelvic and plastic surgeons, endocrinologists, urologists, gynecologists, psychologists, psychiatrists and research specialists established what became to be known as the “gender identity movement” (Pauly & Edgerton, 1986). Transsexualism, defined as the personal intense desire to become the sex opposite to the original sex at birth by hormonal and/or surgical means, became the focus of this new medical subspecialty. In the case of intersexuality, it is a tenet in the field that unmanaged cases of babies who are born with ambiguous genitalia will eventually lead to gender dysphoric individuals at a later developmental
stage. Nevertheless, the clinical management of sex and gender has received strong criticisms within health care fields and beyond (Bloom, 2002; Butler, 2004; Colapinto, 2000; Dreger, 1998; Fausto-Sterling, 2000; Meyerowitz, 2002; Preves, 2003).

Our current knowledge on human embryology has uncovered the molecular cascades, the cellular processes, and the timing of a plethora of biological events, which are required for the sexual differentiation of the body during the first trimester of intrauterine development and has allowed biomedical researchers and physicians to confidently talk about “biological sex.” But based on human embryology principles, the scientific reasoning with regard to the sexual differentiation of the body is erroneously applied to current ideas on gender identity formation. The paradoxical term “embryology of gender” is proposed to refer to the faulty logic that applies biological principles to a social construct.

**SCIENTIFIC PRINCIPLES ON GENDER**

In the Absence of the Y Chromosome, a Gendered Female is Formed

Although it is correct to state that the Y chromosome contains a gene that encodes TDF in mice/TDY in humans and that it induces the formation of the testis during intrauterine development, which ultimately produces a male phenotype through mechanisms that are largely androgen-dependent, it is now clear that there are multiple mechanisms that can produce “maleness.” As an embryologist and historian of science states, “Sex determination in mammals is still a gigantic unsolved puzzle” (Pinto-Correia, 1997, p. 261). Indeed, many regulatory genes participate in the differentiation of the rudimentary gonad as shown in several animal models and, more recently, as validated in humans (for a review see Fleming & Vilain, 2004). Some of these genes include the transcription factors SOX9, SF1, WT1, DAX1, FOXL2, DMRT1/2, and the growth factors WNT4, FGF9, and RSP01. A study of 50 Brazilian sex-reversed individuals concluded that yet unidentified genes must participate on sex-determination as mutations in SRY, DAX1, SF1, and WNT4 failed to account for the sexual variations seen among these 50 individuals (Domenice et al., 2004). But a recent study demonstrated that SOX9 is up-regulated among SRY-negative XX males (Kojima et al., 2008, for an earlier report see Huang, Wang, Ning, Lamb, & Bartley, 1999). The doubling of SOX9 mRNA expression on SRY-negative XX male testes was accompanied by a significant reduction of DAX1 and Ad4BP/SF 1 expression (Kojima et al., 2008). Therefore, a gene other than SRY is sufficient to differentiate the rudimentary gonad into testes. In the case of ovary differentiation, it is now clear that WNT4 represses male-typical reproductive tract formation (for a review
see Kim & Capel, 2006). In fact, mutation of WNT4 in a 46, XX background leads to high androgen levels and absence of Müllerian-derived structures (Biaison-Lauber, Konrad, Navratil, & Schoenle, 2004). Other genes involved in ovarian development include FOXL2 and Rspo1, via β-catenin (Kim et al., 2006, Maatouk et al., 2008, Parma et al., 2006). Therefore, the emergent scenario in the human genetics of sex determination is that dosage effect, threshold requirements, and the timing of expression patterns of multiple genes can differentiate the rudimentary gonad into ovaries or testes. These new data can help us understand the underlying genetic landscape of 75% of sex reversal cases that cannot be explained today according to the prevalent SRY model (for reviews see Vilain & McCabe, 1998, DiNapoli & Capel, 2008).

It is now evident that the TDF (TDY) gene participates but is not essential for male sex determination. Therefore, a conceptual and ideological shift has been proposed, the developmental program for the female requires the active suppression of that for the male. The ideas that the female sex is the “default sex” and the male sex is induced by a single signal are questionable. In addition, we have come used to the notion that the developmental program for sexual differentiation is unitary and that variation(s) from the program leads to malformations and/or ambiguities. But the wide array of human sex configurations documented today favors the idea that multiple biological programs must converge even to create the typical male and female forms. Other models for the sexual differentiation of the body include (a) sex-specific gene activation of over 50 genes before the formation of the gonads (Dewing, Shi, Horvath, & Vilain, 2003) and (b) faster rates for cell proliferation and metabolism for the differentiation of the indifferent gonad into testis instead of ovaries (Mittwoch, 1992).

Gender Must Match the Anatomy of the Sexual Organs

Clitoral and penile sizes that fall outside of the 95% confidence interval that defines normalcy among individuals with the standard chromosomal makeup are produced by biological mechanisms and developmental time frames that are dependent on karyotype background. For instance, high levels of androgens during the first trimester of intrauterine development in a 46,XX background can produce an enlarged clitoris at birth, whereas a micropenis at birth can be produced by disruption of androgen signaling at the gonad level to disruption of hypothalamus-pituitary-gonadal axis signaling to even environmental factors (Chan et al., 2009, Latronico, Costa, Mendoca, & Arnhold, 2005, Mesnag, Clair, Spiroux de Vendômois, & Seralini, 2009, Sahakitrungruang et al., 2009). For the most part, it is assumed that unacceptable genital values will lead to gender dysphoria (Starcevic, 2007).
irrespective of chromosomal background given that the embryological pro-
gram was faulty. Boyle and colleagues (2005) discusses the conflation of
 genitals and gender on the medical desirability for genital surgery. In fact,
 there are boys who develop male gender identity in the absence of gender-
specific genitalia (Zucker, 1999). Therefore, the anatomy of the sex organs
is not a crucial determinant in gender identity as once assumed by medicine
(Ashmed et al., 2004).

Over the years, the clinical management of all forms of 46,XX con-
genital adrenal hyperplasia (CAH) cases has raised many controversies. The
clinical algorithm assumes that most, if not all, 46,XX CAH individuals de-
velop a female gender identity (AAP, 2000, Lee et al., 2006), but there is
evidence that a proportion of these individuals self-initiate a gender change
to male around puberty (Jorge et al., 2008a, 2008b; Dessens, Sliper, & Drop,
2005; Meyer-Bahlburg et al., 1996). But it has not been possible to corre-
late the degree of genital virilization according to the Prader Scale with an
The idea that a large clitoris may produce gender confusion in a girl is
based on the working hypothesis that high androgen levels in a 46,XX back-
ground can lead to male gender identity formation and, perhaps, lesbianism.
But the notion that homosexual males have female-like endocrine profiles
whereas homosexual females have male-like endocrine profiles is outdated
as it has been refuted by numerous studies since the 1970s (for review
see Banks & Gartrell, 1995). Figure 1 shows the disproof of the androgen
hypothesis.

Several conclusions can be drawn by examining these intersex cases
according to clinical diagnosis. First, functional androgen receptors may be
required to secure male gender identity formation among 46,XY individuals
with complete androgen insensitivity syndrome (CAIS) because a 100% of
these cases self-identify as females (reviewed in Jorge, 2007; Byne, 2006;
Wisniewski et al., 2000; Figure 1, left panel). Second, activation of andro-
gen receptors by dihydrotestosterone (DHT) may participate in male gender
identity formation among 46,XY individuals with 5α-reductase syndrome be-
because 37 to 44% of these cases self-identify as females (Cohen-Kettenis, 2005;
Figure 1, middle panel). Third, androgens from adrenal sources in 46,XX in-
dividuals may mediate male gender identity formation because according
to reported cases, a conservative 2 to 10% of 46,XX individuals with con-
genital adrenal hyperplasia (CAH; for review see White & Speiser, 2000)
self-identify as males (Zucker, 1999, Sliper, Drop, Molenaar, & de Muinck
Keizer-Schrama, 1988, Hines et al., 2004; Figure 1, right panel). But even
if one follows the logic of the androgen hypothesis with regard to gender
formation, it cannot be applied to male to female (MtF) or female to male
(FtM) transsex individuals because they seem to have androgen levels that
are concordant with karyotype background (for reviews see Gooren, 2006,
Wilson, 2001).
Gender Formation Follows a Linear Developmental Program

It is a tenet in the field that the development of gender identity results from a combination of unknown genetic factors, prenatal endocrine signaling, and postnatal psychosocial experiences. Can recent neurobiological findings support linear cognitive and endocrine models for gender identity formation? In the human literature, an impressive body of work by Swaab and collaborators has shown that neuroanatomical sex-specific differences are apparent in a number of limbic nuclei in the brain (for review see Swaab, 2004; Swaab, Chung, Krujiver, Hofman, & Ishunina, 2002). In the case of the sexually
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dimorphic nucleus of the preoptic area, it is clear that sex differences are apparent by the fourth year of life. This is of great interest because there is no endocrine signaling that can mediate the onset of such differences at that age. The discovery of factors ZFY and SRY in the hypothalamus and frontal and temporal cortex in adult men but not in women (Mayer, Lahr, Swaab, Pilgrim, & Reisert, 1998) opens up the possibility that a significant array of genes mediate the onset and maintenance of the sexual differentiation of the brain that are independent of gonadal and/or endocrine signaling. In addition, it has been shown that MtF transsexuals have a female-sized nucleus in the sexually dimorphic nucleus of the stria terminalis (BSTc) (Zhou, Hofman, Gooren, & Swaab, 1995, Krujiver et al., 2000). However, it is remarkable that such neuroanatomical sex difference does not become overt until adulthood (Chung et al., 2002), suggesting that function precedes structure with regard to a potential biological correlate of gender identity. It would be advantageous if other research groups around the world replicate and expand these intriguing results. In fact, the production of neuroscientific knowledge on human sexuality from a geopolitical perspective cannot be ignored (Jorge, 2010).

More recently, a study failed to find a functional neurobiological substrate that correlates with gender identity. Specifically, occipitotemporal-, anterior cingulate-, medial prefrontal-, pre- and postcortices, as well the thalams, hypothalamus, and amygdala were all activated on erotic film stimulation among 12 heterosexual males, 12 heterosexual females, and 12 MtF individuals (Gizewski et al., 2009). If a neurobiological correlate of gender identity is ever identified with neuroimaging technology, such correlation will not be informative with regard to which one came first—structural change or neural function? To date, human neuroanatomical data suggests nonlinear relationships between gender and its potential neurobiological correlate.

Nevertheless, recent studies strive to make the unequivocal link between brain structure-function with gender and sexuality. It has been recently reported that homosexual males show brain activation patterns similar to heterosexual females and homosexual females show patterns similar to heterosexual males (Savic & Lindström, 2008). The notion that gay males are like heterosexual females and lesbians are like heterosexual males has consistently been championed by scientific reasoning since the 19th century (Bullough, 1994). Perhaps not surprisingly, this recent study has been interpreted as evidence that sexual preference is established in the womb (Rahman, 2008).

CONCLUSION

Current evidence suggests that if a developmental program for gender identity formation is utilized, such a program will rely on multiple biological
substrates according to karyotype. The time span of such developmental program and the net contribution of each potential biological substrate across development remain unknown. Clinical wisdom has secured “the embryology of gender” as a dogma despite scientific evidence of its inadequacy. Biomedical experts rely on the logic of human embryology as a set of programmed, sequential, and overlapping events to distinguish between a “healthy” and a “sick” gender. The current management of intersexuality and transsexuality assumes that sex (re)assignment will always lead to a gender identity that is congruent with such assignment because “sex = gender” for clinical purposes. This assumption is based on the idea that an unknown developmental program for gender identity formation parallels the sexual differentiation of the body. For instance, the current clinical management of intersexuality is deployed to define the boundaries of what constitutes an acceptable male or an acceptable female. But many gaps in the field do not warrant a biomedical framework to explain and to manage gender.

REFERENCES


CONTRIBUTOR

Juan Carlos Jorge obtained a PhD in Neurosciences from Brandeis University (1997) and has employed rodent models to study sex-specific behaviors since then. In addition, he conducts research on the clinical management of intersexuality from historical and policy perspectives.