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To be Male or Female-That Is the Question [Editorial]

Reiner, William MD

The Johns Hopkins Hospital, Baltimore, Md (Reiner).

Boys will be boys. Or is it quite so simple? In this issue of the Archives, Diamond and Sigmundson [1] report a case with longitudinal insights illustrative of what "proper maleness and femaleness" might be. In a world of socioculturally directed political correctness, this can be a difficult subject to explore. For as we are barraged by media, sexual athletics, and voyeurism on one side, we are awash in sexual activism and gender politics on the other. Yet the fabric of sexuality often seems no more discernible today than it might have been to our forefathers, content as they probably were in their world of proper maleness and femaleness.

The case reported is that of a 46 XY child who was sex reassigned in infancy due to traumatic loss of the penis. This child, at least as his case evolved into early adolescence, is well known within the literature, referenced in innumerable textbooks of pediatrics, psychiatry, and sexuality, [2,3] as an example of successful sex reassignment in early childhood. However, longitudinal data as presented by Diamond and Sigmundson appear to have refuted the conclusions of earlier articles about this child, papers that have formed the crux of sex reassignment theories and clinical decision making for more than 2 decades. This case provides insight into the world of gender identity formation. The data should be critically analyzed in light of other case reports and ongoing studies, [4] as well as in light of neuroscientific advances. [5,6] Future sex reassignment decisions should be made with maximum sophistication in regard to the implications, psychosocial and psychosexual, of brain development as it is influenced by the intrauterine hormonal milieu. In turn, such brain development influences postnatal psychosexual development.

This case is also an exploration of a young patient's life story with its iatrogenic implications and subsequent and ongoing patient self-redirection. This young man represents a case-problem that occasionally confronts pediatricians, pediatric endocrinologists, urologists, child psychiatrists, and psychologists: genital

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abnormalities so severe that sexual function is unlikely to be successful or even satisfactory. The case itself expresses the complexities inherent to the sexual being, with its insights into gender identity, gender role, and sexual orientation. It attests to the necessity of unraveling the neuroscientific foundations of the sexual brain.

Molecular reductionism, psychoanalytic observations, and ethological assessments have to take second position, at least temporarily, to simple but critical longitudinal analyses of children who have been sex reassigned. In essence, we need more data. It may well be that conclusions about sex reassignment as described in much of the literature are erroneous secondary to the conspicuous lack of such longitudinal data and appropriate longitudinal analysis. In fact, present data is increasing that despite great care in rearing these sex-reassigned children as females, some, or perhaps many of them, have strong male tendencies or may even change their assigned sex when they reach 12 to 14 years of age. In other words, anatomical (genital) relatedness and appearance may be less dynamic than the prenatal hormonally differentiated brain. [4-6] Anatomy does not necessarily the man make.

Past clinical decisions about gender identity and sex reassignment when genitalia are greatly abnormal have by necessity occurred in a relative vacuum because of inadequate scientific data. Clinical decisions have been constructed largely on the predicted adequacy of the genitalia for adult sexual function. But the human may not be so easily deconstructed. Sex chromosome anomalies, gender identity disorder, genital malformations, metabolic adrenal or testicular errors—these conditions imply a sexual plasticity of great complexity. Yet that plasticity may be limited to a finite, and perhaps relatively brief, intrauterine androgen exposure, as this case implies. Comprehending the neuroscientific underpinnings of psychiatry and psychology, then, is critical to clinical decision making in such cases. Expanded research is providing new data at perhaps geometrical rates.

First, let us explore a brief history of the science of sexual dimorphism. In 1953, Jost [7] confirmed the hypothesis that testicular chemical (hormonal) factors lead to embryological phenotypic sexual dimorphism. Money [8] has dedicated a large part of his career to exploring the psychological frontiers of abnormal prenatal hormonal milieu and of consequent gender or genital ambiguity. Raisman and Field [9] first demonstrated sexual dimorphism in the brain in 1971. Additional and future studies are expanding our knowledge of brain sexual dimorphism. Yet this roughly 43 years of scientific history has provided only limited understanding of the sexual brain. And gender identity, like sexual orientation, is a complex process in only the initial infancy of scientific understanding.

Evaluation of the structure and metabolic function of the human brain has been difficult, for obvious reasons. Yet some differential dimorphic functions are relatively obvious. For example, sexual behavioral divergence can be observed at all ages. Behavioral and cognitive sexual differences are interpreted variously as manifestations of biology or as fine details of the environment. Biological proponents subscribe to the contribution of the prenatal and postnatal hormonal milieu, while behaviorists are likelier to endorse the psychosocial (postnatal) climate. At present, advanced neuroimaging modalities and postmortem structural evaluations are exploring differences between male and female brain structures. Integrating all of these observable data requires additional and more sophisticated studies.

What can be stated is that the absence of prenatal androgen exposure, whether a child is XX, XO, has an androgen insensitivity syndrome, and so on, may render the brain to the default, or female, position. Within the potential for transformation from the default brain to the virilized brain is the opportunity for errors of incomplete or improperly timed androgen exposure. Such errors, in addition to acquired, sometimes iatrogenic, postnatal injuries, as in the presented case, may lead to the misassignment or reassignment of sex at birth from the genetic sex. These patients provide us an opportunity to further explore the various

contributions to gender role and identity. In particular, they are ideal subjects for a variety of evaluations of central nervous system sexual dimorphism and of prenatal vs postnatal hormonal effects.

For example, a number of studies have assessed 46 XX females with congenital adrenal hyperplasia. The consequences of such varying degrees of exposure to androgens in female embryos and fetuses have been assessed in these children reared as females as they develop into adolescence and adulthood. In my own studies at The Johns Hopkins Hospital, Baltimore, Md, I am following a cohort of fifteen 46 XY males castrated at birth due to severe genital anomalies who are reared unequivocally as females. At present, the 46 XY and 46 XX subjects with congenital adrenal hyperplasia, all reared as females, do not appear to be classically male or female but display masculine characteristics that are in many cases quite striking. Two children in my series, before the age of 12 years, had declared themselves to be male. Three others spontaneously described themselves as the most masculine girl they know. With ongoing studies we are continuing to assess toddler, late childhood, and adolescent psychosocial and psychosexual development in these children.

Somewhat uniquely, these 46 XY female children all seem clearly interested in discussing their sexuality. This willingness should allow us to delineate their precise psychosexual risks and vulnerabilities, as well as protective factors. Thus, we should be able to design interventions for those children with psychosexual developmental anomalies. Such longitudinal assessments may provide insight into appropriate advice for parents of newborns with such conditions based on predictable psychosocial and psychosexual outcomes for that specific condition.

In the end it is only the children themselves who can and must identify who and what they are. It is for us as clinicians and researchers to listen and to learn. Clinical decisions must ultimately be based not on anatomical predictions, nor on the "correctness" of sexual function, for this is neither a question of morality nor of social consequence, but on that path most appropriate to the likeliest psychosexual developmental pattern of the child. In other words, the organ that appears to be critical to psychosexual development and adaptation is not the external genitalia, but the brain. If the brain knows its gender independent of social-environmental influences, then we need to be able to predict what that gender is.

(Figure 1) William Reiner, MD.



Figure 1. William Reiner, MD

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William Reiner, MD

The Johns Hopkins Hospital, Baltimore, Md

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Gender Identity; Genitalia; Penis; Sex Characteristics; Sex Dimorphism; Sex Reassignment

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