Sex Determination, Differentiation, and Identity

TO THE EDITOR: We applaud Reiner and Gearhart (Jan. 22 issue)\(^1\) for highlighting the difficulties of sex assignment but would like to emphasize how their study confirms the complexity of the development of sexual identity,\(^2\) not its biologic determination.

First, the data are subject to alternative explanations. Sexual identity is internal, and thus to assess it from parents’ reports is problematic. Parents may have misinterpreted behavior as reflective of sexual identity. Prenatal androgens facilitate male-typical play, but masculine play is consistent with female identity.\(^3,4\) Second, the decision by 6 of 14 subjects to reassign themselves to the male sex may have arisen not just from androgen exposure, but also in response to complex social conditions, such as a mismatch between behavior and parents’ expectations or peers’ stigmatization.\(^2,5\) Third, the follow-up methods were unsystematic and subjective; interviewers’ expectations were probably conveyed to the participants and introduced into the scoring. This factor may have contributed to identity changes between the initial and final assessments.

These data add to, but do not resolve, the controversy about treating children with intersex conditions and those with discordance between their sexual differentiation and their physical appearance. Treatment must be based on thorough consideration of the data.

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TO THE EDITOR: Reiner and Gearhart report on the sexual identity of 14 genetically male patients with cloacal exstrophy. Six identified themselves as females, two had “unclear” identity, and six identified themselves as males, after learning of their genetic sex. The authors conclude that “neonatal assignment of genetic males to female sex because of severe phallic inadequacy” should be reexamined on the basis of these data.

Some important points are missing. First, the authors report that the subjects who identified themselves as males desired surgical reconstruction of a penis. However, Reiner and Gearhart and a colleague have reported elsewhere that men with bladder exstrophy had psychosocial dysfunction regarding their constructed genitalia, as well as anxiety and mood disorders.1 Time will tell whether the young participants in the current study are able to overcome such obstacles in adulthood. In addition, the authors’ speculation that “prenatal androgens appear to be a major biologic factor in the development of male sexual identity” is not supported. Other groups have not reported male identity in similar children.2,3 Intersex studies also do not support their hypothesis.4,5

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TO THE EDITOR: In their comprehensive review article on sex determination and differentiation, MacLaughlin and Donahoe1 state, “Germ cells are absent . . . in ‘Sertoli-only’ testes of infertile men who have deletions in the long arm of the Y chromosome in the azoospermia factor (AZF) regions that control spermatogenesis.” However, the most common of these deletions, the AZFc interstitial deletion, is often associated with at least some degree of spermatogenesis, even in azoospermic persons; in these patients, haploid germ cells can usually be retrieved by testicular sperm extraction and used for assisted reproduction. In one study, germ cells were found in 30 of 42 patients with an AZFc deletion (71 percent), detected in the seminal fluid or at biopsy or identified after testicular sperm extraction; the most frequent pattern at biopsy in azoospermic patients was arrest of maturation.2 Very similar results have been reported in a subsequent study.3 Thus, in the majority of patients with AZFc deletions, a Sertoli-cell–only pattern is not present.

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DRS. REINER AND GEARHART REPLY: Let us reemphasize several points we make in our article. First, cloacal exstrophy is not an intersex condition: gonads and prenatal sex hormones (and hormone receptors) are typically normal. Removal of the testes at birth and feminizing genitoplasty were performed...
because historically the surgical construction of a phallus has not been feasible. Second, the primary outcome of interest was sexual identity; in our article we discuss comparable studies, but in our view, drawing parallels with studies of children with intersex conditions is fraught with difficulties. Finally, we strongly agree that treatment of children with intersex conditions — and all other children as well — should be based on thorough consideration of the data. Since data tend to be sparse in children with rare conditions (intersex conditions as well as cloacal exstrophy), longitudinal studies are important.

Regardless of their interpretation, however, our data reflect a strong trend toward transition to male sexual identity longitudinally in genetically and hormonally male subjects with cloacal exstrophy who were reared as females; those reared as males have remained male. Syndromic difficulties notwithstanding, none of the subjects living as males have had reported major depression or suicidal ideation since their transition to a male identity.

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Drs. Donahoe and MacLaughlin Reply: The statement to which Dr. Tomasi refers — in its entirety, “Germ cells are absent in the mutant strain of piebald mice and in ‘Sertoli-only’ testes of infertile men who have deletions in the long arm of the Y chromosome in the azoospermia factor (AZF) regions that control spermatogenesis” — is limited to infertile men with testes that contain only Sertoli cells and no germ cells. We meant to imply that the azoospermia factor region of the long arm of the Y chromosome is important for spermatogenesis. We do not discuss detailed differences in azoospermia factor subregions a, b, or c.

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Vasopressin versus Epinephrine for Cardiopulmonary Resuscitation

To the editor: We congratulate Wenzel et al. (Jan. 8 issue)1 on their study of vasopressor treatment for out-of-hospital cardiac arrest. The accompanying editorial by McIntyre urges an immediate change to resuscitation protocols. The American Heart Association and the International Liaison Committee on Resuscitation are engaged in an evidence-based review of the literature on resuscitation, which will culminate in an international consensus conference in January 2005, followed by treatment recommendations. During this process, more than 250 resuscitation experts analyze and debate all the available data on resuscitation. Expert debate is needed in the interpretation of the post hoc subgroup analyses (e.g., analyses of subgroups based on the initial cardiac rhythm and subgroups given the study drug and additional epinephrine) and the most clinically important outcomes (overall survival and survival with a good neurologic outcome). Enthusiasm for an urgent change in resuscitation protocols based on the study reported by Wenzel et al. must be tempered by the lack of a significant difference between the groups in the rates of survival to hospital admission and survival to hospital discharge. Ten of the 20 survivors in the subgroup that received vasopressin and epinephrine were in a comatose or vegetative state or had severe cerebral disability, as compared with 1 of 5 in the epinephrine group. We urge providers to wait for, and to participate in, the international evidence-evaluation process before changing resuscitation protocols.

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