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Gender Identity Outcome in Female-Raised 46,XY Persons with Penile Agenesis, Cloacal Exstrophy of the Bladder, or Penile Ablation

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This review addresses the long-term gender outcome of gender assignment of persons with intersexuality and related conditions. The gender assignment to female of 46,XY newborns with severe genital abnormalities despite a presumably normal-male prenatal sex-hormone milieu is highly controversial because of variations in assumptions about the role of biological factors in gender identity formation. This article presents a literature review of gender outcome in three pertinent conditions (penile agenesis, cloacal exstrophy of the bladder, and penile ablation) in infancy or early childhood. The findings clearly indicate an increased risk of later patient-initiated gender re-assignment to male after female assignment in infancy or early childhood, but are nevertheless incompatible with the notion of a full determination of core gender identity by prenatal androgens.

KEY WORDS: gender dysphoria; gender identity; penile agenesis; cloacal bladder exstrophy; penile ablation.

INTRODUCTION

Clinical policies of gender assignment in newborns with ambiguous genitalia are dependent on (1) the clinicians' theoretical assumptions concerning the determinants of gender, (2) the relative importance attached to outcomes such as gender dysphoria/gender change, fertility, sexual functioning, sexual orientation, and general quality of life, and (3) the medical treatment options available at the time (e.g., sex hormone treatment and specific techniques of genital surgery). The assumptions concerning the determinants of gender are partly based on the results of outcome research on intersex persons, in whom one or more of the biological mechanisms of sexual differentiation are compromised, particularly the prenatal sex-hormonal milieu, which is known to affect both body and brain. Yet, to what extent can results from intersex research be generalized to gender development in non-intersex persons without such prenatal endocrine abnormalities? A strictly experimental test of the impact of biological factors under such circumstances would require random assignment of endocrinologically normal infants (e.g., of chromosomal males), to one of the two genders, along with gender-assignment-conforming genital feminization for female-assigned infants, an approach that would be ethically unacceptable for purposes of research. However, in recent decades, the approach of female gender assignment combined with surgical feminization has frequently been taken for 46,XY patients with one of three medical conditions involving severe genital abnormalities of non-hormonal origin in the hope of improving their quality of life. The three conditions include penile agenesis, cloacal exstrophy of the bladder (and some extreme cases of classical exstrophy of the bladder), and penile ablation (traumatic loss of the penis) in infancy.

Penile agenesis (or aphallia) is characterized by the absence of the penis in the usual position on the abdomen, as part of a developmental pelvic field defect, with urethrorectal communication in most cases, and with variable additional malformations in many, including testicular

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maldescent, renal abnormalities, vesicoureteral reflux, imperforated anus, and musculoskeletal and pulmonary abnormalities (Cendron, 2001). In the most clear-cut cases, neither a penis nor any remnants of penile corpora are found on the abdominal wall or between scrotum and anus; the scrotum is intact, the testicles descended, and the urethra opens near or inside the anus or rectum. The condition also includes patients in whom displaced remnants of the penile corpora can be found in locations between the underside of the scrotum and the anus. In many patients, the location of the urethra facilitates bacterial infection of the urinary tract with associated increased morbidity and mortality; therefore surgical relocation of the urethra is common.

Cloacal exstrophy of the bladder is a severe variant of the bladder exstrophy-epispadias-cloacal exstrophy complex involving an abdominal wall defect and associated with omphalocele, bladder exstrophy, short-gut syndrome, separated pubic bones, and variable additional severe malformations such as spina bifida and clubfoot (Gearhart, 2001). The penis is often aplastic and bifid, and sometimes entirely absent. Cloacal exstrophy in the newborn used to be fatal until Rickham (1960) reported the first surviving case as a result of new surgical techniques. Since then, the rate of survival of such infants into childhood, adolescence, and adulthood has greatly increased, but there is still very significant morbidity and substantial mortality. Classical bladder exstrophy is a less extreme variant from the same disorder spectrum, and in some cases, severe penile malformations are also present.

Penile ablation, or traumatic loss of the penis, in infancy may occur as a result of circumcision accidents, dog bites, deliberate mutilation, and other reasons. The genital development prior to trauma can usually be assumed to have been normal-male, comparable to that in the general population.

In an extension of the optimal-gender policy developed by Money and associates at Johns Hopkins in the 1950s for patients with hormone-abnormality-based intersexuality, various authors recommended gender assignment to female of severe non-hormonal genital abnormalities because of the impossibility of creating a functional penis at that time: for instance, Money (1968, pp. 47–49) and Young, Cockett, Stoller, Ashley, and Goodwin (1971) for penile agenesis; Zwiren and Patterson (1965), Money (1968, p. 53), and Tank and Lindenauer (1970) for cloacal exstrophy; and Money and Ehrhardt (1972, pp. 118–123) for penile ablation.

Female gender assignment/re-assignment of such cases was based on a number of considerations: (1) In most intersex children, gender identity develops in line with gender assignment, if gender assignment is done in infancy. (2) For most people, sexual functioning is very important for their overall quality of life. (3) Historically, surgeons could create a neo-vagina sufficient for intercourse, but not a functional neo-penis (although in recent years, there have been significant improvements in surgical techniques, and the prospects for future developments look promising).

There are also several counterarguments to this approach: (1) The prenatal androgen milieu in these three conditions is usually assumed to be male-typical, given that (pre-surgically) normal testicular function has been shown in such cases (e.g., by direct tests of endocrine function such as stimulation by human chorionic gonadotrophin (hCG) leading to increased testosterone levels in infants with penile agenesis) (e.g., Gautier, Salient, Pena, Imperato-McGinley, & Peterson, 1981) or indirectly, by demonstration of normal testicular histology in infants with cloacal exstrophy (Mathews, Perlman, Marsh, & Gearhart, 1999). (2) Prenatal brain masculinization must therefore be assumed to be male-typical, which is born out by assessments of gender-differentiated behavior in female-raised persons with these conditions (e.g., Meyer-Bahlburg, Ehrhardt, Pinel, & Gruen, 1989; Reiner & Gearhart, 2004; Zucker, 1999). (3) Some patients who were originally assigned or early re-assigned to the female gender are known to have changed their gender to male again. The most widely reported example was the "John/Joan case," originally born male, after a circumcision accident in infancy re-assigned to female during the second year of life, self-reassigned to male in adolescence, and ended in suicide at age 38 years (for references, see Table V). (4) Assignment to the male gender permits retention of the testes, endogenous sex-hormone production, and (with medical assistance) frequently also fertility.

Yet, to what extent do biological factors such as the prenatal sex-hormone milieu contribute to the development of gender *identity*? If biological factors fully determined the sexual differentiation of the brain and of gender identity as a functional outcome, female-assigned 46,XY persons with one of the three non-hormonal genital abnormalities reviewed here should have a male gender identity, when it emerges in preschool age, and maintain it through adulthood. In fact, there should not be any difference in gender identity outcome between female-assigned and male-assigned patients of the same syndrome. The purpose of this article is to review the existing pertinent evidence in the published literature.

METHOD

Medline and PsycINFO were screened for the period 1966 through 2004 for pertinent literature by using as

keywords: penile agenesis, cloacal exstrophy, exstrophy of the bladder, ablatio penis, and penis. For promising titles, the abstracts were screened, and for abstracts with relevant content, the respective articles and chapters, if they could be procured. Also, the reference lists of such articles and chapters were screened for additional pertinent publications. Article languages were limited to English, German, and French. Information was excerpted on patients ages 4 years and over who were not severely mentally retarded, and on whom there was information on the gender to which the person had been assigned between birth and early childhood, and on the gender in which s/he was living at the age when data were collected for the report. Data were excerpted from the articles according to the column categories listed on the tables; in addition, we excerpted some statements pertinent to understanding the gender data.

RESULTS

Tables I–V provide the gender history for the categories of patients under consideration, and Table VI summarizes the data across reports and across syndromes. In the cited reports, the gender in which the patients were officially living can be reasonably inferred. However, in only a few of these reports were gender identity or gender dysphoria systematically assessed.

Penile Agenesis

Table I lists 16 patients with penile agenesis who were assigned to the female gender at birth or re-assigned to female during early childhood. Age at gonadectomy, where provided, varied from birth to 3.9 years. Table VI shows the breakdown by age group at latest report. At that time, 12 were living as females, two as a females with possible gender dysphoria, and two as males. Only four of these patients were adults, i.e., 18 years or older.

Table II provides similar data on 17 patients with penile agenesis who were raised as males. At the latest report, all were living as males. Only 6 of these men were adults (Table VI). The difference in gender outcome between female- and male-raised patients is highly significant ($p \leq .001$, two-tailed, Fisher's Exact Test), regardless of whether the two persons with possible gender dysphoria are included among the ones living as females or the ones living as males.

Cloacal Exstrophy of the Bladder

The gender history in 51 patients with cloacal exstrophy (including one with classical exstrophy) who were early assigned to the female gender is shown in the top portion of Table III.

At the time of the most recent report, 33 were living as females, 7 as females with possible gender dysphoria, and 11 as males, but only 8 were adults (Table VI).

The top portion of Table IV lists 15 patients with cloacal exstrophy raised male. At the time of the most recent report, all were living as males (Table VI). The difference in gender outcome between female- and male-raised patients with cloacal exstrophy is highly significant ($p \leq .001$, two-tailed, Fisher's Exact Test), regardless of whether the seven patients with possible gender dysphoria are included among the ones living as females or the ones living as males.

Classical Exstrophy of the Bladder

The bottom portion of Table III shows the gender history for three patients with classical bladder exstrophy assigned (or early re-assigned) to female. By the time of the most recent report, the two adults were living as males and the one adolescent as a female.

Male-raised patients with classical bladder exstrophy are contained in the bottom portion of Table IV. At latest report, all 279 were living as males (although one, a 12-year old, had possible gender dysphoria); most of these were adults (Table VI). The difference in gender outcome between the male- and female-raised groups also goes into the expected direction, but cannot be statistically tested because of the small sample size of the female-raised group.

Penile Ablation

Table V lists seven patients who suffered a traumatic loss of the penis in infancy or early childhood with subsequent physician-imposed re-assignment to female. Two of these patients had been one of conjoint twins with one set of male genitals who, after separation, was left without genitals. Gonadectomy took place at 6 months to 5-1/2 years of age. At the time of the latest report, four patients (one child, two adolescents, and one adult) were living as females, one (adult) as a female with gender dysphoria, and two (one adolescent, one adult) as males (Table VI). The difference in gender outcome between these seven patients and genitally normal 46,XY children raised male with a lower-bound estimate for transsexual change of 1:10,000 (Bakker, van Kesteren, Gooren,

Table I. Gender History in 46,XY Individuals ≥4 Years of Age with Penile Agenesis and (Re-)Assignment to Female in Infancy or Early Childhood ($N = 16$)

Reference	Country	N	GA at birth	Phys GRA at age	GonX at age	Pat GRA at age	Age (years) at study	Lives as M/F	ID as M/F/other	Gender dysphoria	Comments
Pohlandt et al., 1974	Germany	1	M	to F at 2.5 years[a]	n.i.	—	5.2	F	n.i.	n.i.	Dresses and acts like a girl, accepted by the peer group.
Johnston et al., 1977; Hendren, 1997, Case 1	U.S.A.	1[b]	F	—	10 months	—	22	F	n.i.	n.i.	No coital experience.
Stolar et al., 1987, Case 2	U.S.A.	1	F	—	3 months	—	13	F	n.i.	n.i.	Patient is on estrogen replacement therapy; "participates in school activities and sports."
Oesch et al., 1987	U.K.										
Case 2		1[b]	M	to F at 2 weeks	2 weeks	—	9	F	n.i.	n.i.	
Case 4		1	F	—	3 months	—	≈14	F	n.i.	?	Severe behavior problems during puberty; "male psychological orientation."
Skoog & Belman, 1989, Case 1	U.S.A.	1[b]	M	to F at 2 weeks	2 weeks	—	8	F	n.i.	n.i.	"Apparently well adjusted 8-year-old girl."
Hendren, 1997	U.S.A.										
Case 2		1	F	—	neonatal	—	19	F	n.i.	n.i.	No coital experience.
Case 3		1	F	—	neonatal	—	5.5	F	n.i.	n.i.	
Case 4		1	F	—	in infancy	—	11	F	n.i.	n.i.	"Social behavior . . . is male-like."
Case 5		1	F	—	at birth	—	21	F	F	n.i.	"Completely female in appearance and social orientation."
Dittmann, 1998	Germany	1	F	to M at 4 months, to F at 3.9 years.	3.9 years	to M at 16–22 years.	≈27	M	M	n.i.	Married to woman for 4 years, currently considering options for having children.
Tillem et al., 1998	U.S.A.	3	3F[c]	—	n.i.	—	≥10, ≥ 4, ≥12	3F	n.i.	n.i.	
Evans, Erdile, Greenberg, & Chudley, 1999, Case 2; Zucker, 2005[d]	Canada	1	F	—	n.i.	16	16	M	M	No	Multiple physical anomalies; IQ = 73; ADHD.
Reiner & Kropp, 2004	U.S.A.	1	F[c]	—	n.i.	—	17	F	n.i.	?	"Refused to declare" gender identity.

Note. GA: Gender assignment; GonX: Gonadectomy; Phys GRA: Physician-imposed gender re-assignment; Pat GRA: Patient-initiated gender re-assignment; ID: Identifies; M: Male; F: Female; n.i.: No information; ?: Possible gender dysphoria without patient-initiated gender reassignment

[a] Implemented by parents at age 3.0–3.5 years.

[b] Isolated penile agenesis with the urethral opening near or in anus or rectum; no erectile tissue located.

[c] Age at female assignment not specified.

[d] K. J. Zucker, personal communication, February 26, 2005.

Table II. Gender History in 46,XY Individuals ≥4 Years of Age with Penile Agenesis and Assignment to Male in Infancy ($N = 17$)

Reference	Country	N	GA at birth	Phys GRA at age	Pat GRA at age	Age (years) at study	Lives as M/F	ID as M/F/other	Gender dysphoria	Comments
Drury & Schwarzell, 1935	U.S.A.	1[a]	M	—	—	13	M	n.i.	n.i.	"Played as other children of his age"; "mental development and his manner were about the same as those of the average boy of his age."
Gillies & Harrison, 1948, Case 2	U.K.	1	M	—	—	16	M	n.i.	n.i.	
McCrea, 1942	U.S.A.	1	M	—	—	19	M	n.i.	n.i.	"Very anxious to be married; wants construction of a penis; can masturbate to ejaculation."
Bernardinelli, Mattoso, Albuquerque, & Cordeiro, 1953	France	1[a]	M	—	—	9	M	n.i.	n.i.	Satisfactory relationship with schoolmates.
Attie, 1961	Lebanon	1	M	—	—	22	M	n.i.	n.i.	Concealed erectile tissue. Non-coitally sexually active.[b]
Stoller, 1965, Case 1; Young et al., 1971, Case 1	U.S.A.	1[a]	M	—	—	4	M	M	No	
Stoller, 1965, Case 2; Young et al., 1971, Case 2	U.S.A.	1[a]	M	—	—	15	M	M	No	Long hospitalizations; homosexual games, fantasies, dreams; marked psychiatric problems.
Kessler & McLaughlin, 1973	U.S.A.									
Case 1		1[a]	M	—	—	≈11	M	M	No	
Case 2		1	M	—	—	22	M	n.i.	n.i.	Homosexual; severe psychiatric problems.
Lisa et al., 1973	C.S.S.R.	1	M	—	—	11	M	n.i.	n.i.	"His role as that of a boy was clearly defined."
Rosenblum & Turner, 1973	U.S.A.	1[a]	M	—	—	45	M	n.i.	n.i.	Never seen a physician in 45 years; "satisfactory" marital relationship.
Gautier et al., 1981, Case 1	Dominican Republic	1	M	—	—	6	M	n.i.	n.i.	Play observations: Prefers boys' toys and games, and male playmates.
Oesch et al., 1987, Case 5	U.K.	1	M	—	—	9	M	n.i.	n.i.	
Choudhury & Maji, 1993	India	1[a]	M	—	—	10	M	n.i.	n.i.	"Has accepted his genital deformity."
Ciftci et al., 1995	Turkey	1	M	—	—	13	M	M	n.i.	Died at 13 of medical problems.
Mutaf, 2001	Turkey									
Case 1		1	M	—	—	35	M	n.i.	n.i.	Penile reconstruction at age 31.
Case 2		1	M	—	—	24	M	n.i.	n.i.	Penile reconstruction at age 22.

Note. GA: Gender assignment; Phys GRA: Physician-imposed gender re-assignment; Pat GRA: Patient-initiated gender re-assignment; ID: Identifies; M: Male; F: Female; n.i.: No information

[a] Isolated penile agenesis with the urethral opening near or in anus or rectum; no erectile tissue located.

[b] Urethral meatus on a small protuberance below the scrotum about 1.5 cm from the anterior margin of the anus. When sexually aroused, there is an erectile body under the skin extending for 10 cm from the perineum up to and over the pubis. "Fully satisfies his frequent sexual desires by masturbation or by friction with female partners." "Absence of the penis has not caused the patient any psychologic or emotional upset."

Table III. Gender History in 46,XY Individuals ≥4 Years of Age with Cloacal or Classical Bladder Exstrophy and (Re-)Assignment to Female in Infancy or Early Childhood ($N = 54$)

Reference	Country	N	GA at birth	N Pat GRA	Pat GRA at age (years)	Age (years) at study	Lives as M/F	ID as M/F/other	Gender dysphoria	Comments
					Cloacal bladder exstrophy ($N = 51$)					
Hayden, Chapman, & Stevenson, 1973, Case 1	U.S.A.	1	1F	—	—	5	1F	n.i.	n.i.	
Meyer-Bahlburg et al., 1989	U.S.A.	2	2F	—	—	8, 12	2F	2F	No	
Lund & Hendren, 1993	U.S.A.									
Case 1		1	1F	—	—	8	1F	n.i.	n.i.	
Case 4		1	1F	—	—	4	1F	n.i.	n.i.	
Hendren, 1997, p. 1473	U.S.A.	1	1F	—	—	Adult	1F	n.i.	n.i.[a]	
Slijper et al., 1998, p. 135	The Netherlands									
Case 1		1	1F	—	—	≥6	1F	—	Yes	GID since age 4 years, ODD since age 6 years.
Case 2[b]		1	1F	—	—	≥15	1F	n.i.	No	"Deviant gender role"; no GID; sex problems since age 15 years; mental retardation.
Tillem et al., 1998	U.S.A.	3	3F	—	—	≥5, ≥18, ≥20	3F	n.i.	n.i.	The oldest is sexually active.
Zucker, 1999, pp. 42–44	Canada	1	1F	—	—	12	1F	1F	No	
Schober et al., 2002 (see also Baker Towell, & Towell, 2003)	U.K.	5	5F	—	—	5–15	5F	5F	n.i.	"More masculine typical gender role behavior in childhood."
Zderic et al., 2002, p. 140	U.S.A.	7[c]	7F			n.i.	4F	n.i.	n.i.	
						20s	1F	—	likely[d]	
						30s	1F	—	likely[d]	
				1 to M	7	≥7	1M	n.i.	n.i.	
Reiner & Gearhart, 2004	U.S.A.	14	14F			9–19	5F	5F	—	
						14–16	3F	—	3F?	
				4 to M	5, 7, 7, 7	8–11	4M	4M	n.i.	
				2 to M	12, 18	20–21	2M	2M	n.i.	

Reiner & Kropp, 2004	U.S.A.	9[e]	9F			5–17	5F	5F	n.i.	
				4 to M	n.i.	7–10	4M	4M	n.i.	
Zucker, 2005[f]	Canada	4								
Case 1			1F	—	—	4	F	F	No	
Case 2			1F	—	—	7	F	—	Yes	
Case 3			1F	—	—	12	F	F	No	
Case 4			1F	—	—	17	F	F	No	"Intellectually delayed."
					Classical bladder exstrophy ($N = 3$)					
Feitz et al., 1994	The Netherlands	1	1F	1 to M	52[g]	52–55	1M	1M	n.i.	"Definite male behavior."
Stein et al., 1994	Germany	1	1M→F[h]	1 to M	after puberty	> 18	1M	n.i.	n.i.	
Tillem et al., 1998	U.S.A.	1	1F[i]	—	—	≥ 16	1F	n.i.	n.i.	

Note. GA: Gender assignment; Pat GRA: Patient-initiated gender re-assignment; ID: Identifies; M: Male; F: Female; n.i.: No information; GID: Gender identity disorder; ODD: Oppositional defiant disorder.

[a] Satisfactory coitus with a bowel vagina.

[b] 2 additional cases are listed without further details.

[c] One additional adult F-assigned patient has "severe developmental delays."

[d] Both "have experienced significant gender identity issues"; one chronically depressed, with "hospitalization following suicidal ideations"; both are "most comfortable in lesbian relationships."

[e] One of the F-assigned patients had classical bladder exstrophy.

[f] K. J. Zucker, personal communication, February 26, 2005.

[g] "Kept home since birth"; "presented for treatment after the death of both parents."

[h] Physician re-assigned to F at 4 years and castrated.

[i] Age at female assignment not specified.

Table IV. Gender History in 46,XY Individuals ≥4 Years of Age with Cloacal or Classical Bladder Exstrophy and Assignment to Male in Infancy ($N = 294$)

Reference	Country	N	GA at birth	N Pat GRA	Pat GRA at age (years)	Age (years) at study	Lives as M/F	ID as M/F/other	Gender dysphoria	Comments
					Cloacal bladder exstrophy ($N = 15$)					
Howell et al., 1983	U.S.A.	1	1M	—	—	19	1M	n.i.		Died at age 19 years, probable suicide.
Husmann et al., 1989	U.S.A.	8	8M	—	—	3–22	8M	n.i.	n.i.[a]	
Lund & Hendren, 1997, p. 1366, Unnumbered Case	U.S.A.	1	1M	—	—	28	1M	n.i.	n.i.[b]	
Reiner & Gearhart, 2004	U.S.A.	2	2M	—	—	12, 19	2M	2M	No	
Reiner & Kropp, 2004	U.S.A.	2	2M	—	—	7–18?	2M	2M	n.i.	
Zucker, 2005[c]	Canada	1	1M	—	—	12	1M	1M	No	
					Classical bladder exstrophy ($N = 279$)					
Fineman, 1959, 1963	U.S.A.	8	7M	—	—	3.5–26	7M	n.i.	7 n.i.	
			1M	—	—	12	1M	—	1M?[d]	
Cogan et al., 1975, Case 2	U.S.A.	1	1M	—	—	15.5	1M	n.i.	n.i.	Isolated, depressed.
Lattimer et al., 1978	U.S.A.	11	11M	—	—	17–30	11M	n.i.	n.i.	
Woodhouse, Ransley, & Williams, 1983	U.K.	51	51M	—	—	18–44	51M	n.i.	n.i.	29 married or in steady relationships.
Duckro, Purcell, Gregory, & Schultz, 1985	U.S.A.	1	1M	—	—	7	1M	n.i.	n.i.	
Mesrobian, Kelalis, & Kramer, 1986	U.S.A.	53	53M	—	—	n.i. (23 "post-pubertal")	53M	n.i.	n.i.	14/23 could achieve satisfactory intercourse.
Zabbo & Kay, 1986	U.S.A.	35	35M	—	—	≥18	35M	n.i.	n.i.	
Feitz et al., 1994	The Netherlands	10	10M	—	—	17—55[e]	10M	n.i.	n.i.	
Stein et al., 1994	Germany	30	30M	—	—	18–40[e]	30M	n.i.	n.i.	
Avolio et al., 1996	U.S.A.	25	25M	—	—	18–53	25M	n.i.	n.i.	
Ben-Chaim, Jeffs, Reiner, & Gearhart, 1996	U.S.A.	16	16M	—	—	18–42	16M	n.i.	n.i.	10 participated in intercourse.
Diseth et al., 1998	Norway	15	15M	—	—	11–20[e]	15M	n.i.	n.i.	
Reiner, Gearhart, & Jeffs, 1999	U.S.A.	14	14M	—	—	14–19	14M	14M	No	
Stjernqvist & Kockum, 1999	Sweden	7	7M	—	—	6–18	7M	n.i.	n.i.	
El Khader et al., 2003	Morocco									
Case 1		1	1M	—	—	21	1M	n.i.	n.i.[f]	
Case 3		1	1M	—	—	25	1M	n.i.	n.i.[g]	

Note. GA: Gender assignment; Pat GRA: Patient-initiated gender re-assignment; ID: Identifies; M: Male; F: Female; n.i.: No information.

[a] 4 post-pubertal: 1M married and coitally active; 2M without erectile capacity;1M unable to penetrate because of small penile size; 3 in psychiatric treatment.

[b] "Very angry, frustrated"; "normal sexual drive, but . . . ill equipped for coitus."

[c] K. J. Zucker, personal communication, February 26, 2005.

[d] This 12-year-old boy played "the role of a cute little girlish child, but he kept all of his thoughts and feelings to himself."

[e] Age or age range provided includes additional categories of patients not listed in this table.

[f] Not coitally active.

[g] Not coitally active; relationship problems.

Table V. Gender History in 46,XY Patients ≥4 Years of Age with a Childhood History of Traumatic Loss of the Penis and Gender Re-assignment to Female ($N = 7$)

Reference	Country	N	GA at birth	Age at penile loss	Phys GRA to F at age	GonX at age	Pat GRA to M at age	Age (years) at study	Lives as M/F	ID as M/F/other	Gender dysphoria	Comments
Money & Ehrhardt, 1972, pp. 118–123; Money, 1975, 1998a, 1998b; Diamond, 1982; Diamond & Sigmundson, 1997; Colapinto, 2000	Canada	1	1M	7 months	17 months. Fem. op. at 21 months	21 months	15 years.	≥33 years	1M	1M	No	One of two male identical twins. Committed suicide at 38 years (New York Times, 2004).
Filler, 1988; Zucker, 1999[c]	Canada	1[a]	1M	5.5 years	5.5 years	5.5 years	—	12 yrs	1F	1F	n.i.	
O'Neill et al., 1988, Case 8; Diamond, 1999	U.S.A.	1[a]	1M	During 3rd year	During 3rd year	During 3rd year	—	10 years (O'Neill et al., 1988)	1F	n.i.	Wishes GRA (Diamond, 1999)	At follow-up statement (Diamond, 1999) ≥20 years.
Gearhart & Rock, 1989, Case 1	U.S.A.	1	1M	"Just after birth"	Early infancy	23 months	—	≥17 years	1F	n.i.	n.i.	"Well adjusted," sexually active.
Gearhart & Rock, 1989, Case 2; Bradley et al., 1998	Canada	1	1M	2 months	2–7 months. Fem. op. at 7 months	7 months	—	26 years	1F	1F	No	Tomboy in childhood; required psych. counseling before vaginoplasty in adolescence.
Gearhart & Rock, 1989, Case 4	U.S.A.	1	1M	2 days	1–6 months. Fem. op. at 3 years	6 months	—	>3 years ?	1F	n.i.	n.i.	
Ochoa, 1998, Case 2	Colombia	1	1M	6 months	Infancy. Fem. op. at 5 years[b]	6 months	≥14 years	≥14 years	1M	n.i.	n.i.	

Note. GA: Gender assignment; Phys GRA: Physician-imposed gender reassignment; Pat GRA: Patient-initiated gender reassignment; ID: Identifies; M: Male; F: Female; n.i.: No information; Fem. op.: Feminizing surgery.

[a] One of conjoint male twins with one set of male genitals who, after separation, was left without genitals.

[b] When "a normal feminine identity process" was "demonstrated" in psychiatric follow-up.

[c] Note added in proof: According to the *Globe and Mail* of June 25, 2005, an article by Jan Wong, entitled Twin Peaks, reports that the second patient (Filler, 1988; Zucker, 1999) listed on Table V of this article is now 23 years old and lives as a man (p. F4).

Table VI. Number of 46,XY Persons (by Clinical Category and Early Gender Assignment) Living as Females or Males at the Most Recent Report ($N = 388$)

	4.0–11.9 years		12.0–17.9 years		≥18.0 years		No individual age specified		Total	
Category	F	M	F	M	F	M	F	M	F	M
Penile agenesis										
GA-F	7	0	2 + 2?	1	3	1	—	—	12 + 2?	2
GA-M	0	7	0	4	0	6	—	—	0	17
Cloacal exstrophy										
GA-F	10 + 2?	9	10 + 3?	0	4 + 2?	2	9	0	33 + 7?	11
GA-M	0	0	0	2	0	3	0	10	0	15
Classical exstrophy										
GA-F	0	0	1	0	0	2	—	—	1	2
GA-M	0	1	0	1 + 1?	0	159	0	117	0	278 + 1?
Penile ablation										
GA-F	1	0	2	1	1 + 1?	1	—	—	4 + 1?	2
Total										
GA-F	18 + 2?	9	15 + 5?	2	8 + 3?	6	9	0	50 + 10?	17
GA-M	0	8	0	7 + 1?	0	168	0	127	0	310 + 1?

Note. GA: Gender assignment (or early-childhood re-assignment); F: Female, M: Male; ?: Possible gender dysphoria without patient-initiated gender reassignment.

& Bezemer, 1993) is highly significant ($p < .001$, point-probability method; Fleiss, Levin, & Paik, 2003, pp. 37–39).

Summarized Data

Table VI summarizes the data within and across syndromes. As the bottom section shows, of the female-assigned patients of childhood age, 69% (including those with possible gender dysphoria) or 62% (excluding those) were living as females, of those of adolescent age 91% (including those with possible gender dysphoria) or 68% (excluding those), of those of adult age 65% or 47%, and of those whose age could not be categorized 100%, altogether across all ages 78% or 65%. By contrast, all male-raised 46,XY patients were living as males in all age groups, and only the report on one of these suggests a possible gender dysphoria. The differences in gender outcome between male-raised and female-raised patients are significant in each age category as well as in the total sample (for the latter, $p \leq .001$, two-tailed, Fisher's Exact Test), even if the patients with gender dysphoria are included among those with the other gender.

DISCUSSION

The main findings can be summarized as follows: (1) The majority of 46,XY individuals with presumably normal-male prenatal hormonal milieu, non-hormonal anatomic abnormalities of the genitals, and female gender assignment at birth or in early childhood, have not changed gender to male and, for those living as females, gender dysphoria or an explicit wish to change gender have rarely been reported or suspected. This is so across all age categories, although there is a modest trend of an increasing number of such individuals switching to male with advancing age. Even by adulthood, however, at least about half maintained their female gender, including patients who were fully aware of their medical history.

These data do not support a theory of full biological determination of gender identity development by prenatal hormones and/or genetic factors, and one must conclude that gender assignment and the concomitant social factors have a major influence on gender outcome. On the other hand, a number of female-raised individuals did change gender to male and others developed a possible gender dysphoria, which indicates that gender assignment does not dictate gender outcome either. Thus, in the conditions described here, female gender assignment of 46,XY infants and young children carries a risk of later patient-initiated gender change to male that is considerably higher than the risk of patient-initiated gender change to female in male-raised patients, no example of which has been reported in any of the publications we have examined. The risk is also much higher than the rate of gender change (transsexualism) in the general population (maximum population estimate for transsexualism in a Western country has been reported as 1:10,000 in men and 1:30,000 in women (Bakker et al., 1993).

These findings need to be considered with caution, however, because of significant methodological caveats. One caveat is that the number of published cases assigned to the female gender and followed into childhood and adolescence is very small, and that the subgroup with follow-up into adulthood is even smaller. The syndromes are rare, 46,XY individuals assigned to the female gender even more so, and the logistics of long-term follow-up are formidable, especially in a mobile society such as the U.S. The longer the follow-up, the more loss to follow-up occurs, with possible attendant selection biases.

Moreover, it is conceivable that cases involving patient-initiated gender change are more likely to be published than the others, given the fact that some investigators in this area are specifically searching for such cases (e.g., Diamond, 1997). On the other hand, some patients who initiate gender change may fault their physicians for past decisions on gender assignment and genital surgery and are less likely to participate in follow-up studies endorsed by these same physicians. In either situation, sample representativeness becomes a problem (see also Zucker, 2002).

Another aspect of these data that calls for caution in drawing definitive conclusions is the poor quality of the assessment methods used in most reports. Apart from Zucker (1999), hardly any investigators used systematic instruments for the dimensional assessment of gender identity and gender dysphoria. As is widespread in clinical practice, it seems that a person was assumed to live in the gender he or she appeared to present her- or himself during clinical visits. The few exceptions are some very detailed psychiatric clinical case descriptions (e.g., Bradley, Oliver, Chernick, & Zucker, 1998; Stoller, 1965). This critique applies even to one of the potentially most important studies in this area, the recent report by Reiner and Gearhart (2004), which has serious methodological flaws despite the elegance of covering a complete clinic sample for the age group selected. Behavioral masculinization was descriptively inferred from a few selected individual items although the protocol's quantitative scales would have permitted dimensional comparisons with other samples. The crucial data on gender dysphoria and gender change were mostly based on unsystematic follow-up communications with the parents and not on evaluations of the patients themselves. Most of the gender changes listed in this study were reported at variable periods of time after the systematic research protocol had been administered. The assessments were not done in masked fashion nor were masked co-raters or other forms of independent verification used. It is also remarkable that most of the cases of gender change to male in Table V come from this report as well as from one other report by the same first author (Reiner & Kropp, 2004), which makes future replication by independent investigators all the more important.

Given the unsatisfactory status of assessments of gender identity and gender dysphoria used in most studies, an underreporting of gender identity problems among the published cases seems possible, especially in younger patients. In view of the young age of many of the published patients, one also can expect some additional cases to change gender in later years. Perhaps some children already harbor an internal gender identity different from the assigned gender, but because of parental pressure or in compliance with parental expectations, they do not let the interviewers in on it. This rationale may apply to Reiner and Gearhart's two patients with cloacal exstrophy whose declaration of male gender was not accepted by their parents, and to the one patient each in Reiner and Gearhart (2004) and Reiner and Kropp (2004) who refused to discuss her (?) gender identity with the interviewer. It may also have applied to the patient with classical exstrophy who was raised female but underwent a gender change to male at age 52 years after both his parents had died (Feitz, van Grunsven, Froeling, & de Vries, 1994). As a clinician working with intersex children who have gender problems, or with non-intersex children with gender identity disorder (GID), I have repeatedly experienced such secrecy, especially on first contact, but after some rapport building, the child usually starts disclosing.

There are also isolated cases in the intersex literature of adult women who were internally certain that they were men, but nevertheless maintained an overt female gender role (e.g., Rösler & Kohn, 1983, pp. 669–670, patient V-18), presumably in order to avoid the social repercussions associated with gender change. It is conceivable that such developments could also occur in patients with the syndromes described in this article, although we are not aware of a single published case with documentation of this type of concealment. One can plausibly assume, however, that such developments are rare, and that the majority of individuals with the conditions reviewed here who were female-assigned and living as females did indeed have a core female gender identity.

By contrast, it seems that most, if not all, individuals with these conditions raised female showed marked masculinization of gender-role *behavior* where such data are available (e.g., Bradley et al., 1998; Colapinto, 2000; Meyer-Bahlburg et al., 1989; Reiner & Gearhart, 2004; Schober, Carmichael, Hines, & Ransley, 2002; Slijper, Drop, Molenaar, & de Muinck Keizer-Schrama, 1998; Zucker, 1999), and most of those old enough were noted to report a sexual attraction to women (e.g., Colapinto, 2000; Reiner & Gearhart, 2004; Reiner & Kropp, 2004; Zderic,

Canning, Carr, Kodman-Jones, & Snyder, 2002) or bisexuality (Bradley et al., 1998). (Data on sexual orientation are even more limited in number and assessment quality than data on overall gender role and gender change and were, therefore, not summarized in the Results section.) Thus, in these three syndromes, gender-differentiated *behavior* (including sexual orientation) appeared to be masculinized in most cases, while core gender *identity* development appeared much more heterogeneous.

The marked masculinization of behavior seen in these female-assigned 46,XY persons with one of the three non-hormonal conditions of genital abnormalities should not be interpreted as a sign of masculinized core gender identity. Unfortunately, the fact that DSM-IV lists behavioral criteria for GID in non-intersex children of preschool or elementary school age has sometimes led to the misinterpretation of such behaviors as components of gender identity itself. However, as we have learned from 46,XX girls with CAH, marked masculinization of gender-differentiated *behavior* is not synonymous with GID, gender uncertainty, or a persistent desire to change gender (Meyer-Bahlburg et al., 2004). The behavioral DSM criteria of gender identity disorder of childhood were introduced to facilitate the diagnosis in non-intersex children who are intimidated by parental pressure or the presence of a strange interviewer/clinician from openly admitting their gender identity confusion or disorder, at a time when systematic assessment approaches were not yet available. However, with appropriate rapport building and the use of systematic assessment tools (see the article by Zucker [2005] in this Special Section) such children usually do disclose their gender confusion or dysphoria.

The behavioral masculinization commonly seen in female-raised patients is most likely a result of the prenatal normal-male sex-hormonal milieu in the conditions under consideration here (Hines, 2002). Why, then, do some of these patients change gender and others do not? Many urological investigators appear to believe that the well-documented neonatal testosterone surge in normal 46,XY males from about the second week of life after a full-term birth through about the fifth or sixth month of age plays a role in the development of male gender identity and, therefore, emphasize the importance of early orchidectomy to prevent androgen "imprinting" of the brain in female-assigned patients (e.g., Ciftci, Şenocak, & Büyükpamukçu, 1995; Johnston, Yeatman, & Weigel, 1977; Oesch, Pinter, & Ransley, 1987; Stolar et al., 1987). In the published data reviewed here, the timing of orchidectomy was highly variable. In the patients with penile agenesis, it varied from neonatal age to 3.9 years. While the only patient with manifest gender change happened to have a history of very late orchidectomy, other cases with definite (Johnston et al., 1977) or probable (Pohlandt, Kühn, Teller, & Thomä, 1974) late orchidectomy did not change gender or show gender dysphoria (Table I). All of the female-reassigned cases of penile ablation (Table V) experienced gonadal loss after the period of the neonatal testosterone surge; nevertheless, most lived as females. For the female-raised cloacal exstrophy patients, case-specific data on the age at orchidectomy were rarely provided. However, Mathews et al. (1999) report a mean age of orchidectomy of 6 months with a range of 0–20 months, i.e., both before and after the neonatal testosterone surge, for 15 patients at Johns Hopkins Hospital, which must have included many of the patients examined by Reiner and Gearhart (2004). This variability probably applies to patients with cloacal exstrophy treated elsewhere as well, which makes it likely that a substantial number of the patients living as females were late-orchidectomized. Even excluding the cases with cloacal exstrophy, however, the published data do not suggest a clear relationship of gender outcome with the timing of orchidectomy and, thereby, exposure of the developing brain to the neonatal testosterone surge. This conclusion would be in line with the findings in the rhesus monkey, the primate most studied in regard to gender development, where most of the gender-behavior related androgen effects take place during the prenatal period, while the elimination of the neonatal testosterone surge only results in somewhat delayed puberty and a somewhat lower sex drive in adulthood (Eisler, Tannenbaum, Mann, & Wallen, 1993; Mann, Akinbami, Gould, Paul, & Wallen, 1998; Mann, Akinbami, Gould, Tanner, & Wallen, 1993).

In psychiatry and psychology, the formation of identity, including gender identity, has always been seen as a psychological process. In classical psychoanalytic theory, the awareness of one's genitals was thought to play a major role in this process, but this assumption was undermined by the observation that, in male-raised 46,XY infants with penile agenesis, a male gender identity can be formed in the absence of a penis (Stoller, 1965). In recent decades, a major body of empirical evidence has led to detailed theories of the normative development of gender (Ruble & Martin, 1998), especially its cognitive components (Martin, Ruble, & Szkrybalo, 2002), refined conceptualizations of gender identity (Egan & Perry, 2001), and the relation of gender identity to other aspects of self-concept and social status (e.g., Yunger, Carver, & Perry, 2004). There is every reason to assume that the processes and psychosocial factors involved in normative gender development also contribute to development of all aspects of gender, including gender dysphoria and gender change in persons with intersexuality and related conditions. Additional factors, however, may come into

play in the latter situation, particularly the awareness of an atypical biological condition and medical history. To what extent does the disclosure of this information to the patient play a role in gender identity development and final gender outcome? Certainly, some physicians consider it extremely important to withhold from these patients information on their biological maleness in terms of sex chromosomes and original gonadal status or the early assignment/re-assignment history, because of the "potentially disastrous psychological effect" (Hendren, 1997). In addition, many parents persistently prevent their children from learning this information accidentally, as also we have observed in some of our own patients. Early disclosure may indeed have an effect on gender decisions in some patients. For instance, Reiner and Gearhart (2004) stated that four of their children with cloacal exstrophy "declared male identity after their parents revealed to them that their birth status was male." In our clinical work with intersex families, we have the impression that it depends on the developmental stage of a child to what extent such disclosure will affect the child's identity. Perhaps that information is particularly powerful at the stage of early to mid-adolescence, i.e., pubertal maturation, when certain aspects of brain growth accelerate (Giedd, 2004; Thompson & Nelson, 2001), the brain is re-organized (Sisk, Schulz, & Zehr, 2003), and somatic development has a striking salience for the developing youngster. By contrast, if such information is not disclosed before young or middle adulthood, the person may have already developed a more stable self image and/or social niche that s/he is less likely to break out of in response to such disclosure, similar to the refusal of or withdrawal from late-onset growth-hormone or sex-hormone treatment that has been observed in some late adolescent or young adult patients with growth-hormone deficiency or with Turner's syndrome (for references, see Meyer-Bahlburg, 1990).

In regard to gender identity development, the situation for individuals with the syndromes under discussion here is quite different when they have been raised as males from the outset. There is not one published male-raised case of a patient-initiated gender change to female and only one case of possible gender dysphoria. This may reflect underreporting, given that systematic assessment procedures were even less frequently employed under these conditions. Even if these findings are accurate, however, they do not necessarily imply that the overall quality of life after male assignment is better. For instance, Howell, Caldamone, Snyder, Ziegler, and Duckett (1983) reported on a cloacal exstrophy patient suspected of having committed suicide, Feitz et al. (1994) quoted a patient with classical exstrophy who "would advise parents who are confronted with known bladder exstrophy during pregnancy to seek termination of the pregnancy," and there were both individual and group reports that referred to significant psychiatric problems, isolation, and withdrawal of male-raised patients with penile agenesis (e.g., Kessler & McLaughlin, 1973; Stoller, 1965), cloacal exstrophy (Husmann, McLorie, & Churchill, 1989; Lund & Hendren, 1993), and classical exstrophy (Cogan, Becker, & Hofmann, 1975; Diseth, Bjordal, Schultz, Stange, & Emblem, 1998). Whether assignment to the female gender increases or diminishes quality-of-life problems and psychopathology in these conditions is unknown. Much more systematic assessments are needed than what is presented in most of these reports to permit a systematic comparison of male- and female-assigned patients in this regard.

One important aspect of the quality of life in adulthood with implications for gender identity is sexual functioning. The differential prognosis for sexual functioning is an important criterium for gender assignment under the optimum-gender policy. The pertinent outcome data for the syndromes reviewed here are inconsistent. Reiner and Gearhart (2004) and Reiner and Kropp (2004) emphasize, albeit without detailed data, that their older 46,XY subjects with cloacal exstrophy who were male assigned or re-assigned reported heterosexual dating and, at least some of them, heterosexual activity, but the ones living in the female gender role seemed sexually inexperienced. Also, other investigators have provided a number of positive statements concerning the sexual activity of individual male-raised or male-reassigned patients (e.g., for penile agenesis: Attie, 1961; Dittmann, 1998; Rosenblum & Turner, 1973; for cloacal bladder exstrophy: Husmann et al., 1989; for penile ablation: Colapinto, 2000, pp. 194–195). On the other hand, some of the few older adolescent or young adult 46,XY women also were reported to be sexually active (for cloacal exstrophy: Hendren, 1997, p. 1473; Tillem, Stock, & Hanna, 1998; Zderic et al., 2002; for penile ablation: Bradley et al., 1998; Gearhart & Rock, 1989, Case 1), while a number of male-raised patients appeared to have significant sexual problems (e.g., for cloacal exstrophy: Husmann et al., 1989; Lund & Hendren, 1993). Thus, the outcomes are mixed. Unfortunately, the published data on sexual functioning are so incomplete and their quality so low that a definitive conclusion on the relative merits of female versus male assignment of these categories of patients in terms of sexual functioning is not possible.

Future research in this area also needs to differentiate sexual avoidance (e.g., because of body image problems), especially in patients with multiple obvious physical abnormalities such as a urethrostomy or colostomy, from more specific anatomic and neuroanatomic problems of

genital functioning. Great variability is to be expected. For instance, some male-raised patients with penile agenesis who have at least remnants of the penile corpora appear to have retained libido and orgasmic/ejaculatory capacity (e.g., Attie, 1961; McCrea, 1942; Rosenblum & Turner, 1973). By contrast, Stoller (1965) described a male-raised patient who apparently had no remnants of the penile corpora. That patient was experienced in sexual games with other males and some unusual form of self-masturbation, but "has never been able to have an orgasm," "has no genital, perineal, oral, or anal sexual sensations analogous to the genital excitement of normal men but simply feels an increased body tenseness that gradually exhausts itself." In order to understand the differences in sexual functioning between different subcategories of patients with penile agenesis, specific neuroanatomic studies of the erotic innervation of the reproductive tract and pelvic floor in such patients are needed to complement the recent advances in the understanding of the developmental neuroanatomy of the normal urogenital tract (Baskin et al., 1999; Baskin, Lee, & Cunha, 1997; Yucel & Baskin, 2003; Yucel, de Souza, & Baskin, 2004) and a first report on the neuroanatomy of the pelvis in an infant with cloacal exstrophy (Schlegel & Gearhart, 1989).

In conclusion, the findings from this review clearly indicate an increased risk of later gender change to male in persons with non-hormonal genital defects after female assignment, but they are not compatible with the view of a full determination of core gender identity by prenatal androgens. It also seems that absence of salient gender dysphoria in childhood does not preclude gender change at a later stage of development. Predictors of gender change remain unclear. Clinical gender decisions also need to consider prospects of sexual functioning, reproductive capacity, and overall quality of life. Whether long-term quality of life in these conditions is better after female gender assignment or male gender assignment remains unsettled.

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