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How Sexually Dimorphic Are We? Review and Synthesis

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ABSTRACT The belief that *Homo sapiens* is absolutely dimorphic with the respect to sex chromosome composition, gonadal structure, hormone levels, and the structure of the internal genital duct systems and external genitalia, derives from the platonic ideal that for each sex there is a single, universally correct developmental pathway and outcome. We surveyed the medical literature from 1955 to the present for studies of the frequency of deviation from the ideal male or female. We conclude that this frequency may be as high as 2% of live births. The frequency of individuals receiving "corrective" genital surgery, however, probably runs between 1 and 2 per 1,000 live births (0.1–0.2%). Am. J. Hum. Biol. 12:151–166, 2000.

Among primates, humans exhibit a modest sexual dimorphism with regard to characters such as body size or voice timbre (Fedigan, 1982). With respect to sex chromosome composition, gonadal structure, hormone levels, and the structure of the internal genital duct systems and external genitalia, however, we generally consider *Homo sapiens* to be absolutely dimorphic. Biologists and medical scientists recognize, of course, that absolute dimorphism is a Platonic ideal not actually achieved in the natural world. Nonetheless, the normative nature of medical science uses as an assumption, the proposition that for each sex there is a single, correct developmental pathway. Medical scientists, therefore, define as abnormal any deviation from bimodally distributed genitalia or chromosomal composition (Conte and Grumbach, 1989). If, however, one relinquishes an a priori belief in complete genital dimorphism, one can examine sexual development with an eye toward variability rather than bimodality.

Conte and Grumbach (1989) list more than 25 diagnoses affecting sexual differentiation. While the incidence of some individual medical syndromes is fairly well established, the overall frequency of intersexuality is a matter of dispute. Fausto-Sterling (1993a,b) cited a figure attributed to John Money that the frequency of intersexuality might be as high as 4% of live births, but Money (1993) responded that he never made such a claim. In fact, no well-documented overview of the frequency of intersex exists at present, and it is this lacuna that we address in the present article. The question is of interest to students of human development, medical practitioners, and human biologists, among others. Recently, the practice of surgically altering the genitals of intersexual infants to conform to assumptions about absolute dimorphism has been questioned (Fausto-Sterling, 1995/1996; Post, 1995/1996; Sandberg, 1995/1996; Walcutt, 1995/1996; Diamond, 1996; Zucker, 1996; Diamond and Sigmundsen, 1997; Kessler, 1998). Thus, both because of a theoretical interest in human sexual dimorphism and medical questions about the treatment of intersexuals, it is important to provide a frequency baseline for the varied events which lead to intersexuality.

METHODS

We surveyed the medical literature from 1955 to the present for studies of the fre-

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quency of deviation from the ideal male or female. For a few rare syndromes, we considered the literature which predates 1955. Our sources included population surveys, genetic studies, case surveys from individual medical practitioners, and environmental population studies. In addition to Medline as a starting point, government documents, bibliographies in textbooks, previously located review articles, and specific articles provided additional sources. We did not exclude any articles which contained frequency estimates derived from an unselected population. Rather, where appropriate we indicate the limitations of particular publications.

We define the typical male as someone with an XY chromosomal composition, and testes located within the scrotal sac. The testes produce sperm which, via the vas deferens, may be transported to the urethra and ejaculated outside the body. Penis length at birth ranges from 2.5 to 4.5 cm (Flatau et al., 1975); an idealized penis has a completely enclosed urethra which opens at the tip of the glans. During fetal development, the testes produce the Mullerian inhibiting factor, testosterone, and dihydrotestosterone, while juvenile testicular activity ensures a masculinizing puberty. The typical female has two X chromosomes, functional ovaries which ensure a feminizing puberty, oviducts connecting to a uterus, cervix and vaginal canal, inner and outer vaginal lips, and a clitoris, which at birth ranges in size from 0.20 to 0.85 cm (Oberfield et al., 1989). In this article, we ask how often development meets these exacting criteria for males and females.

The literature which reports the frequencies of syndromes that produce intersexuality varies in quality and quantity. In some cases there are multiple surveys with large numbers replicated over many years and in many different geographical locations. In others no data exist with which to estimate frequency, while in still others the lack of better data dictated reliance on one or a small number of reports of uncertain quality. In each case the available data are presented. The strength or weakness of an estimate is also indicated.

"SEX" CHROMOSOME COMPOSITION

Individuals with XXY, XO, XYY, XXYY, XX males, and 47,XXX females comprise the most frequently encountered deviations from an XX (female) or XY (male) chromosomal make-up. An XO condition produces individuals with female external genitalia and streak gonads which are incapable of fetal or pubertal gonadal hormone synthesis and a variety of somatic alterations, while 47,XXX girls develop secondary sex characteristics at puberty and are sometimes fertile (Buckton, 1983). XXY individuals diagnosed with Klinefelter syndrome have external male genitalia, small testes, impaired spermatogenesis, and frequent gynecomastia. XXYY individuals are considered karyotypic variants of Klinefelter syndrome (Conte and Grumbach, 1989; Zinn et al., 1993). XYY males are taller, on average, than XY males, and commonly exhibit underdeveloped testes (Vogel and Motulsky, 1979). Recent work, however, suggests that many 47,XXY and 47,XYY males are undiagnosed because they present no symptoms which prompt a chromosomal analysis (Abramsky and Chapple, 1997). The category of XX males, which involves the translocation or deletion of a submicroscopic section of the sex determining region of the Y chromosome, is morphologically and genetically heterogeneous (López et al., 1995).

Table 1 summarizes the results of 17 studies of the frequencies of XXYY, XX (male), 47,XXX, and XYY individuals at birth. The total frequency ranges from 0.002 to 2.15/1,000 live births, with a mean of 0.639/1,000 and a standard deviation of 0.665. The mean/1,000 live births and standard deviations for each of the non-XX, non-XY chromosome compositions listed in Table 1 are 0.155 (0.185) for XXYY, 0.05 (0.019) for XX males, 0.47 (0.364) for 47, XXX, and 0.639 (0.665) for XYY.

In 24 different estimates of the frequency of Klinefelter syndrome (XXY), the incidence ranges from 0 (out of 3,890 births) to 2.13/1,000 births. The mean incidence for all 24 studies is 0.922/1,000 live births with a standard error of 0.102 (Table 2). The 18 different estimates for the population frequency of XO chromosome constitution are shown in Table 3. The incidence ranges from 0.0 for five small studies (sample size of less than 3,993) to 1.67/1,000 live births. The mean is 0.369/1,000 live births, with a standard error of 0.111. Recent data showing that not all Turner patients present with XO identifiable by traditional karyology suggest that the incidence calculated

*TABLE 1. Incidence of XXYY, XX(male), 47,XXX and XYY births in 17 published surveys**

Location	Year	Total # surveyed	XXYY	XX male	47,XXX	XYY	Incidence/1,000 live births	Method	Reference
Edinburgh	1964	20,725	1		11		0.575	Bs[a]	Maclean et al., 1964
Geneva	1968	8,184			1		0.122	Bs	Mikamo, 1968
London	1969	2,081				4	1.922	K	Sergovich et al., 1969
New Haven	1970	4,366			3	3	1.374	K	Lubs, 1970
Toronto	1974	73,229	1	2	2		0.068	Bs/K	Bell, 1974
Moscow	1974	2,500			1		0.400	K	Bochkov et al., 1974
Winnipeg	1975	13,939			5	7[b]	0.861	K	Hamerton et al., 1975
Ontario	1976	930				2	2.150	K	Lin et al., 1976
Denver	1976	40,371			12		0.297	Bs/K	Goad et al., 1976
USA	1977	13,751		1			0.073	K	Walzer et al., 1977
Tokyo	1978	12,319				3	0.244	K	Higurasi et al., 1979
Edinburgh	1979	23,196		1	11		0.517	Bs/K	Ratcliffe et al., 1979
Edinburgh	1980	3,993			3	4	0.002	K	Buckton et al., 1980
USA	1982	19,675			25		0.001	K	Schreinemacher et al., 1982
Telemark	1982	1,830				1	0.546	K	Hansteen et al., 1982
Belgium	1988	77,000	32[c]				0.416	K	Kleczkowska et al., 1988
Denmark	1991	34,910	5[d]	2	18	20[b]	1.289	K	Nielsen, 1991
Average total/1,000 live births (SD)			0.155 (0.185)	0.05 (0.019)	0.470 (0.364)	0.865 (0.740)	0.639 (0.665)		

*K, karyotype. B_5, buccal smear.
[a]Excludes perinatal deaths.
[b]Includes mosaic and nonmosaic.
[c]Includes 25 people with more than two X chromosomes.
[d]Includes four xx/xy mosaics.

from previously published studies may be an underestimate (Zinn et al., 1993).

Androgen insensitivity in XY individuals

Disruption of fetal hormonal metabolism in XY fetuses results most commonly from defects in androgen receptors. Clinical features range from a fully female external phenotype, with a blind-ending vagina and little axillary hair development, to a masculine phenotype with azoospermia and elevated levels of luteinizing hormone (Griffin and Wilson, 1989). Estimates of the frequency of complete androgen insensitivity (AIS) range from 0.049 to 0.016/1,000 male (Bangsbøll et al., 1992; Griffin and Wilson, 1989). In addition, 1–2% of girls with inguinal hernias may have androgen insensitivity (Griffin and Wilson, 1989). Jagiello and Atwell (1962) estimate the frequency of inguinal hernias in girls at 8/1,000 female births. Hence, the frequency of complete AIS may be 0.12/1,000 female births. Averaging the estimates for male births and combining them with the estimate for female births yields a figure of 0.076/1,000 live births. There are no solid estimates of the frequency of partial AIS, but Griffin and Wilson (1989) suggest that it is one-tenth as common as complete AIS. Using these estimates the rate would be 0.0076/1,000 live births.

Griffin and Wilson (1989) cite three other forms of AIS: 5α-reductase deficiency, Reifenstein syndrome and Infertile Male syndrome. The first two produce externally visible intersexuality, while those with Infertile Male syndrome are phenotypically male. 5-α-Reductase deficiency is quite common in a number of populations, ranging from Central America to Vietnam (Mendoca et al., 1996). Indeed, more than 50 families with over 100 affected individuals have been reported. However, no population or gene frequencies are available (Conte and Grumbach, 1989; Mendoca et al., 1996; Al-

*TABLE 2. Incidence of XXY births in 24 published surveys**

Location	Year	Total # surveyed	Total XXY[a]	Incidence/1,000 live births	Method	Reference
Winnipeg	1959	3,715	5	0.135	Bs	Moore, 1959
Bombay, India	1962	3,890	0	0	?	Subray and Prabhaker, 1962
Seattle[b]	1964	1,954	2	1.02	?	Paulsen et al., 1964
Edinburgh	1964	20,725	20	0.97	?	Maclean et al., 1964
Geneva	1968	8,184	6	0.73	?	Mikamo, 1968
London, England	1969	2,081	1	0.481	K	Sergovich et al., 1969
USA	1970	3,543	5	1.411	K	Gerald, 1970
New Haven	1970	4,366	4	0.916	K	Lubs, 1970
Germany	1973	1,000	2	2.00	?	Golob, 1973
Dehli	1973	3,100	3	0.97	?	Verma et al., 1973
Toronto	1974	73,229	43	0.59	?	Bell, 1974
Moscow	1974	2,500	2	0.800	K	Bochkov et al., 1974
Winnipeg	1975	13,939	6	0.430	K	Hamerton et al., 1975
Ontario	1976	930	1	1.075	K	Lin et al., 1976
Denver	1976	40,371	23	0.57	?	Goad et al., 1976
USA	1977	13,751	10	0.727	K	Walzer, 1977
Edinburgh	1979	23,196	21	0.91	?	Ratcliffe et al., 1979
Tokyo	1979	12,319	2	0.162	K	Higurasi et al., 1979
Edinburgh	1980	3,993	6	1.503	K	Buckton et al., 1980
Telemark	1982	1,830	1	0.546	K	Hansteen et al., 1982
Northeast (USA)	1982	19,675	20	1.017	K	Schreinemacher et al., 1982
Germany	1984	13,168	28	2.126	K	Murken, 1984
Denmark	1991	34,910	27	0.773	K	Nielsen, 1991

*?, Not specified; K, karyotype; Bs, buccal smear.
[a]Mosaic and nonmosaic.
[b]Study reported only male births; we doubled the denominator to estimate total births.

*TABLE 3. Incidence of XO births in 18 published surveys**

Location	Year	Total # surveyed	Total[a]	Incidence/1,000 live births	Method	Reference
Edinburgh	1964	20,725	4	0.400	Bs	Maclean et al., 1964
Geneva	1968	8,184	2	0.509	Bs	Mikamo, 1968
London	1969	2,081	0	0	K	Sergovich et al., 1969
?	1970	3,543	0	0	K	Gerald, 1970
New Haven	1970	4,366	1	0.458	K	Lubs, 1970
Dehli	1973	3,100	1	0.644	Bs	Verma et al., 1973
Toronto	1974	73,229	5	0.141	Bs	Bell, 1974
Moscow	1974	2,500	2	1.671	K	Bochkov et al., 1974
Winnipeg	1975	13,939	2	0.296	K	Hamerton et al., 1975
Denver	1976	40,371	27	1.370	Bs	Goad et al., 1976
Ontario	1976	930	0	0	K	Lin et al., 1976
Edinburgh	1979	23,196	1	0.105	Bs	Ratcliffe et al., 1979
Tokyo	1979	12,319	1	0.168	K	Higurasi et al., 1979
Edinburgh	1980	3,993	0	0	K	Buckton et al., 1980
Telemark	1982	1,830	0	0	K	Hansteen et al., 1982
New York State	1983	76,474	9	0.118	K	Hook, 1983
Denmark	1991	34,910	8	0.229	K	Nielsen, 1991

[a]Mosaic and nonmosaic.
*Bs, buccal smear; K, karyotype.

Attia, 1996). Similarly, no such estimates exist for Reifenstein or Infertile Male syndrome. Aiman and Griffin (1982) report evidence of androgen resistance in more than 40% of men with no other obvious cause for severe oligo- or azoospermia.

Congenital adrenal hyperplasia

The most common cause of intersexuality in XX females is congenital adrenal hyperplasia (CAH), a label which covers a heterogeneous set of genetically inherited alterations in steroid biosynthesis. The work on CAH has been thoroughly reviewed (Laue and Rennert, 1995; New et al., 1989; Newfield and New, 1997; Pang and Clark, 1990, 1993). Table 4 presents a summary. Although not all forms of CAH result in ambiguity at birth, the table includes estimates for any manifestations which alter sexually dimorphic presentation at any time during the life cycle. The classic form of 21-

TABLE 4. Incidence of 21-OHase (classic) in 36 published surveys

Location and subpopulation	Sample size	Date	Frequency/1,000 live births	Reference
Part A: Case surveys				
Switzerland	1,516,299	1980	0.0646	Werder et al., 1980
France	41,073,409	1985	0.031	Bois et al., 1985
France	13,921,803	1985	0.0356	Bois et al., 1985
Switzerland		1988	0.198	Pang et al., 1988
Canada		1988	0.038	Pang et al., 1988
Austria		1988	0.111	Pang et al., 1988
US (Wisconsin)		1988	0.067	Pang et al., 1988
Switzerland		1988	0.0542	Pang et al., 1988
Hungary	27,497,606	1989	0.0023	Thompson et al., 1989
Canada	346,000	1989	0.0689	Thompson et al., 1989
Hungary	2,119,727	1988	0.033	Sólyom, 1989
Japan	585,000	1990	0.0228	Pang and Clark, 1990
Kuwait	540,000	1990	0.001	Lubani et al., 1990
Sweden	1,727,928	1990	0.0827	Thilén and Larsson, 1990
Israel (Jewish population)		1986–1991	0.0333	Sack et al., 1997
Israel (Arab population)		1986–1991	0.1250	Sack et al., 1997
US		1993	0.025	Pang and Clark, 1993
Average (SD)	0.0584 (0.0495)			
Range	0.001–0.198			
Part B: Mass screening				
Alaska-Caucasian	13,733	1982	0.0728	Pang et al., 1982
Hungary	968,303	1989	0.0537	Sólyom, 1989
France (La Reunion)	31,472	1990	0.315	Pang and Clark, 1990
US (Illinois)	357,825	1990	0.0838	Pang and Clark, 1990
Portugal	100,000	1990	0.070	Pang and Clark, 1990
Scotland	119,960	1990	0.0583	Pang and Clark, 1990
Washington	255,527	1990	0.0547	Pang and Clark, 1990
Japan	2,523,948	1990	0.0223	Pang and Clark, 1990
Switzerland	65,823	1993	0.0911	Pang and Clark, 1993
Germany	12,500	1993	0.08	Pang and Clark, 1993
Italy	133,198	1993	0.09	Pang and Clark, 1993
Sweden	660,000	1993	0.0848	Pang and Clark, 1993
France (regional)	270,060	1993	0.0778	Pang and Clark, 1993
Canada	50,000	1993	0.06	Pang and Clark, 1993
Brazil	82,870	1993	0.1327	Pang and Clark, 1993
Spain	206,875	1993	0.058	Pang and Clark, 1993
Alaska-Yupik	3,740	1993	3.47	Pang and Clark, 1993
Native Alaskan	12,131	1993	1.236	Pang and Clark, 1993
New Zealand	536,915	1995	0.0428	Cutfield, 1995
Texas (white)	872,648	1989–1995	0.064	Therrell et al., 1998
Texas (Hispanic)	764,101	1989–1995	0.069	Therrell et al., 1998
Texas (African American)	253,854	1989–1995	0.0236	Therrell et al., 1998
Texas (other)	46,410	1989–1995	0.1293	Therrell et al., 1998
Average for screening (SD)	0.280 (0.738)			
Without Yupik or Native Alaskan	0.083 (0.06)			
Without Yupik, Native Alaskan, or La Reunion	0.0709 (0.0288)			

hydroxylase deficiency is the most common, and the frequency estimates are the most reliable. Pang and Clark (1990, 1993; Pang et al., 1988) have published detailed comparisons of estimates obtained from case reports in large population databases, as well as from more recently available mass screening programs. The direct screening programs have resulted in higher estimates for the condition than have the more traditional population surveys. In both instances, however, one striking fact emerges:

TABLE 5. Incidence of 11-B-hydroxylase (classic) in six published surveys

Location and subpopulation	Sample size	Method	Frequency/1,000 live births	Reference
Switzerland	1,516,299	Case	0.0032	Werder et al., 1980
France	13,921,803	Case	0.0071	Bois et al., 1985
Hungary	2,119,727	Case	0.0018	Sólyom, 1989
Kuwait	540,000	Case	0.0055	Lubani et al., 1990
Sweden	1,727,928	Case	0.0005	Thilén and Larsson, 1990
Moroccan Jews		Gene frequency estimates	0.1667	Rösler et al., 1992
		Mean (SD)	0.031 (0.067)	
		Range	0.0005–0.1667	
		Mean (SD) and range without Moroccan Jews	0.00362 (0.00267) 0.0005–0.0071	

the gene frequency for 21-hydroxylase deficiency varies significantly among populations. Worldwide and national estimates must be considered in this light.

Table 4 presents data obtained from original sources and from reviews by Pang and Clark (1990, 1993). The average frequency for 21-hydroxylase deficiency using case surveys is 0.0584 ± 0.0495 and a range of 0.001–0.198/1,000 live births. The corresponding statistics from mass screening (and minus the very high incidence among Yupik Eskimos) are 0.083 ± 0.060, and a range of 0.0428–0.315 per 1,000 live births. The worldwide frequencies do not include the Yupik data (3.47/1,000 live births) and the incidence in La Reunion, France (0.315/1,000 live births). It does not seem obvious, however, that it was appropriate to eliminate the La Reunion data; even though the number is high, it is in the same order of magnitude as other data used in the calculation (e.g., Brazil). Therefore, we averaged the numbers arrived at with and without the La Reunion data, arriving at a worldwide frequency of classic CAH due to 21-hydroxylase deficiency of 0.0770/1,000 live births.

Tables 5 and 6 contain data concerning the rarer enzyme deficiencies leading to CAH. The average incidence for 3-β hydroxysteroid dehydrogenase is 0.00068/1,000 live births, while that for 11-β-hydroxylase (minus the very high frequency found in Moroccan Jews) is 0.00362/1,000 live births (0.00267) with a range of 0.0005–0.0071/1,000. The one available frequency estimate for 17-alpha hydroxylase places the number at 7×10^{-5}/1,000 live births.

Finally, the unusual case of nonclassic or late onset 21-hydroxylase deficiency needs consideration. Nonclassic CAH is defined as a deficiency that arises anytime after the first 5 years of life. In childhood, such cases may come to medical attention because of premature signs of puberty, hirsutism, and clitoral growth. In adults, the signs can include hirsutism, menstrual disorders, and clitoral enlargement (Eldar-Geva et al., 1990; Pollack et al., 1981). Speiser et al. (1985) used estimates of gene frequencies for late onset 21-hydroxylase deficiencies to calculate the incidence of affected individuals in several different localities and ethnic groups. While the incidence of late-onset 21-hydroxylase varies widely among different ethnic groups, its overall frequency is extremely high. The calculated frequencies are 37/1,000 among Ashkenazi, 19/1,000 among Hispanics, 16/1,000 among Yugoslavs, 3/1,000 among Italians, and 0.01/1,000 among a mixed Caucasian population. Although the estimates are widely accepted and cited (Arnaut, 1992; Eldar-Geva et al., 1990; White et al., 1987; Newfield and New, 1997). We could not locate articles confirming the reported frequencies of Speiser et al. (1985). Thus, while we use this estimate in the final calculation of nondimorphism, future reports may contain modifications of the estimates.

Vaginal and penile agenesis

XY babies born with testes, but complete absence of a penis, are extremely rare, probably occurring only once in a million births (Bansal and Singh, 1990; Kumar et al., 1986; Rupprecht et al., 1989). In contrast, complete or partial vaginal agenesis is fairly common. Harkins et al. (1981) report that 6 of 26 patients with vaginal agenesis had AIS, while the remainder had Meyer-Rokitansky-Küster-Hauser (MRKH) syndrome, which is characterized by aplasia of

TABLE 6. Incidence of rare forms of classic CAH published surveys

Location and subpopulation	Type	Sample size	Method	Frequency/1,000 live births	Reference
Switzerland	3-Beta Ohase (classic)	1,516,299	Case	0.0019	Werder et al., 1980
France	3-Beta Ohase (classic)	13,921,803	Case	0.0007	Bois et al., 1985
France	17-alpha-hydroxylase	13,921,803	Case	0.00007	Bois et al., 1985
Kuwait	3-Beta Ohase (classic)	540,000	Case	0.0055	Lubani et al., 1990
Average for 3-Beta	0.00068/1000				

the vagina, typical female secondary sexual characteristics, attenuated fallopian tubes, and typical ovaries and female karyotype (Chervenak et al., 1982). To avoid "double counting" of AIS patients, we report complete estimates of vaginal agenesis incidence, but in the final calculations, assume that only 77% of these comprise an otherwise unmeasured deviation from the usual pathway of female development.

Unfortunately, the literature on the incidence of vaginal agenesis appears more promising than it actually is. Most articles quote an incidence of 1/4,000 to 1/5,000 births. When one traces the citations, however, they all lead to two publications. Engstad (1917, p. 330), reporting on cases encountered in a private practice, writes: "From my own experience I should judge that we might expect to find one case in about five thousand." Bryan et al. (1949) note the Engstad report and cite a paper by Owens, who reported six cases in 125,000 hospital admissions (0.048/1,000). From their own clinical experience, Bryan et al. (1949) estimate a frequency of 1/4,000 female patients (0.25/1,000). Currie (1974) reported that between July 1969 and 1973 there were 5,189 deliveries and 2,988 gynecological admissions at a USAF Medical Center. Of the total of 8,177, there were two records of complete or partial vaginal agenesis. In the most recent independent estimate, Willemsen and Dony (1988) estimated that 1/30,000 living Dutch-born women have Mayer-Rokitansky syndrome. Recognizing the limited basis of the present knowledge of the frequency of vaginal agenesis, we use the figure of 1/4,500. Assuming that 77% of these are due to unique causes, the final incidence is 0.1694/1,000 live births. Since congenital absence of the vagina can be asymptomatic, this may be an underestimate.

Hormone-producing tumors and exogenous sex hormones

Hormone-producing tumors are relatively rare, and no population-level estimates of incidence exist. They can, however, cause virilization of adult women, including voice changes, clitoral growth, and hirsutism. In addition, they have been known to cause fetal masculinization during pregnancy (Hensleigh and Woodruff, 1978; Ireland and Woodruff, 1976; Verhoeven et al., 1973). It is also difficult to ascertain the frequency of genital alterations caused by treatment with progestins during pregnancy. A recent meta-analysis of studies done on births following first trimester exposure to low doses of sex hormones, especially from oral contraceptives, suggests little or no danger to genital development (Raman-Wilms et al., 1995). However, earlier studies focused on much higher doses of progestin, used in efforts to avoid miscarriage. Not only were the doses greater in these cases, but treatment occurred well into the second trimester of pregnancy, a time when one might especially expect an effect on the development of external genitalia (Steinberger and Odell, 1989). Not all progestin-treated pregnancies result in fetal masculinization. However, the rate for high-dose, second-trimester treatments is probably quite high (Burstein and Wasserman, 1974; Ishizuka et al., 1962; Jacobson, 1962). Unfortunately, no good estimates exist of the number of individuals currently living with iatrogenically induced genital alterations. There is also no presently reliable way to know whether the practice of treating threatened miscarriages with progestins continues with any frequency today, although the data presented in Table 7 (section on True Hermaphrodites) suggest that the practice has significantly declined.

True hermaphrodites and idiopathic mixed genitalia

There are no published population-wide estimates of the frequency of true hermaphrodites (individuals born with both testicular and ovarian tissue). However, a number of surgeons and endocrinologists, who specialize in the treatment of nonconforming

TABLE 7. Comparative numbers of true hermaphrodites and other forms of intersexuality

Year	Hypospadias	CAH	Gonadal dysgenesis (mixed and pure)	AIS: complete and partial	True herma-phrodites	Exo-genous	Vaginal agenesis or atresia	Penile agenesis	Cloacal malforma-tions	Idio-pathic	XY: micro-penis	Virilizing adenoma	Reference
1960		87	71	47	3	22							Wilkins, 1960
1965		100	116	66	4	18				20			Wilkins, 1965
1967		39	5	7	1	16							Jones and Wilkins, 1967
1974		28			6							1	Kumar et al., 1974
1986	19	29	7	1	1	3	11		8				Currarino, 1986
1987	0	24	8	5	6	1				14			Lobe et al., 1987
1987		4	1	2	1						1		Oesterling et al., 1987
1989		21		10	2								Lorge et al., 1989
1990	4	6	6	5	2			1					Pinter and Koxatolanyi, 1990
1991		14	1	7						3			Abdullah et al., 1991
1991	6	32	10	10	3		4		4	5			Coran and Z., 1991
1992	6	46	8		4	9	1	2	6	7			Newman et al., 1992
1992		12	5	7	38	9							Danso and Nkrumah, 1992
1993		38	23	12									Ramani et al., 1993
1994	39(total)	4		1									Greenfield et al., 1994
Total		442			84								
% of CAH (all entries)					19%					11%			
% of CAH minus rows 7 (possible duplicate) and 13 (African data)					13%								

TABLE 8. Frequencies of various causes of nondimorphic sexual development

Cause	Estimated frequency/100 live births
Non-XX or non-XY (except Turner or Klinefelter)	0.0639
Turner	0.0369
Klinefelter	0.0922
Subtotal for chromosomal difference	0.193
Androgen Insensitivity syndrome	0.00760
Partial Androgen Insensitivity syndrome	0.000760
Classic CAH (omitting very high frequency population)	0.00770
Late-onset CAH	1.5
Subtotal of known hormonal causes	1.516
Vaginal agenesis	0.0169
True hermaphrodites	0.0012
Idiopathic	0.0009
Total	1.728

physical sex types, report on the distribution of patients. Data extracted from 14 such reports are summarized in Table 7. Although different reports come from different specialties, rendering the referral bias for any one report great, by analyzing a large number of such reports and making use of the fact that the frequency of CAH is well established, an estimate of the order of magnitude of the occurrence of true hermaphroditism can be obtained.

Particularly striking in Table 7 are the data of Danso and Nkrumah (1992), who reported 38 true hermaphrodites in a database of 71 patients with ambiguous genitalia. Although the reported numbers seem inordinately high, the data are consistent with other reports suggesting high frequencies of true hermaphroditism in southern Africa (Krob et al., 1994; Ramsay et al., 1988). In addition, some forms of true hermaphroditism are familial (Kuhnle et al., 1993; Skordis et al., 1987; Slaney et al., 1998), which opens the possibility that, as with other inherited forms of sexual ambiguity, there may be pockets, perhaps even large geographical regions, with relatively high frequencies of true hermaphroditism.

The data in Table 7 were used to estimate the relative frequency of true hermaphroditism. First we compared the number of true hermaphrodites summed from all 14 reports with the number of cases of CAH (19%). Then we considered the percentage after eliminating the report from southern Africa, as well as the older of two reports which may contain duplicate data. The latter ratio is 11% and, splitting the difference, the estimate of true hermaphroditism equals 15% of the frequency of classic 21-OHase CAH. Using a figure of 0.0779/1,000 live births for classic CAH, the average frequency of true hermaphroditism is on the order of 0.0117/1,000 live births, or one in 100,000.

The data in Table 7 also allow the calculation of the frequency of idiopathic sexual ambiguity. Using the same reasoning as for true hermaphrodites, the birth of a sexually ambiguous child from unknown causes is about 0.009/1,000 live births.

Overview

This article began by asking how frequently members of the human population deviate from a Platonic ideal of sexual dimorphism. A summary of the frequencies of known causes of sexual ambiguity based on Tables 1–7 appears in Table 8. The grand total is 1.728% of live births. Because there are no general population-level frequency estimates for iatrogenic variations in genital anatomy, penile agenesis, and disorders of 5-α-reductase biosynthesis and some of the rarer forms of CAH, the data in Table 8 provide a minimal estimate. However, except for certain restricted populations the frequencies of such events are quite rare and would probably not greatly influence the overall estimate. The two most frequent deviations from complete sexual dimorphism arise from nondimorphic sex chromosome conditions and from alterations in steroid hormone metabolism. Although this generalization holds for a generic Euro-American, Caucasian population, it is inappropriate in certain geographical settings. Thus, there is strong evidence that CAH is very frequent among native Alaskans and that true hermaphroditism is surprisingly common in southern Africa. Because of the Eurocentric nature of most medical data, there may well be other large population groups worldwide which exhibit substantial frequencies of intersexuality.

TABLE 9. Incidence of hypospadias

Location	Date	Total sample	Incidence/1,000 live births	Reference
Rochester, MN	1954	8,716	3.901	Harris and Steinberg, 1954
Brooklyn	1958	30,398	0.921	Shapiro et al., 1958
International	1966	416,695	0.586	Stevenson et al., 1966
Liverpool, UK	1968	91,176	1.228	Smithells, 1968
US, multiregion	1968	35,680	2.41	Chung and Myrianthopoulos, 1968
South Wales, UK	1972	92,982	1.097	Roberts et al., 1972
Sweden (general)	1973	550,000	0.949	Kallen, 1973
Sweden (Uppsala)	1973	96,733	1.158	Pettersson, 1973
Jerusalem	1973	59,261	3.004	Harlap, 1973
Athens	1973	74,390	1.949	Trichopoulos et al., 1973
Atlanta, GA	1974	137,179	2.012	CDC statistics cited in (Avellan, 1975)
Jerusalem	1975	11,036	3.625	Harlap, 1973
Sweden	1975	480,607	1.386	Avellan, 1975
Latin American	1981	432,839	0.764	Neto and Paz, 1981
Emilia-Romagna, Italy	1986	42,156	3.985	Calzolari et al., 1986
Denmark	1986	801,241	0.975	Kallen et al., 1986
Hungary	1986	1,992,773	1.827	Kallen et al., 1986
Italy	1986	303,674	1.798	Kallen et al., 1986
Mexico	1986	162,105	0.352	Kallen et al., 1986
South America	1986	902,984	0.693	Kallen et al., 1986
Spain	1986	334,970	1.797	Kallen et al., 1986
Sweden	1986	896,954	2.085	Kallen et al., 1986
Alsace, France	1990	118,265	1.488	Stoll et al., 1990
Atlanta, GA	1993	?	3.0	Paulozzi et al., 1997
USA	1993	?	3.8	Paulozzi et al., 1997
Mean	1.87	SD	1.105	Range: 0.352–3.985

Estimates that combine categories

The approach used to estimate intersexuality, at all levels, from the chromosomal and hormonal to the anatomical, is plagued by the uncertainties inherent in the medical literature. Therefore, we derived a second type of estimate from statistics on the frequencies of cryptorchidism (undescended testes) and hypospadias (the incomplete closure around the urethra of the embryonic genital folds). These estimates serve as an order of magnitude check of the preceding calculations. Hypospadias and cryptorchidism both result from a variety of underlying causes of intersexuality (Aaronson et al., 1997; Aarskog, 1971; Gearhart et al., 1990; Gill et al., 1989; Gill and Kogan, 1997; Rajfer and Walsh, 1976). A U.S. Army survey in the 1940s (Rajfer and Walsh, 1976) found that 0.7% of the adult male population had cryptorchidism. Scorer and Farrington (1971) noted that the incidence of cryptorchidism is higher at birth and declines throughout the first year of life to 0.8% of male births (or roughly 0.4% of all births).

Table 9 contains an overview of the data for hypospadias. The mean incidence of hypospadias, averaged from over 20 studies over four decades, is 1.87/1,000 live births, with a standard deviation of 1.105 and a range of 0.352–1.043. The data on hypospadias may be further subdivided into the incidence of severe and medium types (urethral opening in the perineal region or along the shaft of the penis) and minimal types (urethral opening between the corona and the tip of the glans penis) (Sweet et al., 1974). Indeed Fichtner et al. (1995) have recently shown widespread variation in the meatal opening along the length of the glans penis. The authors suggested that such variation, sometimes classified as minimal or mild hypospadias, is normal and surgery in such cases unwarranted. It is difficult to obtain absolute estimates of the rates of minimal, medium, and severe hypospadias, because not all publications record the data in the same manner, and some contain numerical discrepancies. Nevertheless, the ratio of minimal to medium and severe hypospadias is about 3:1. If, as Fichtner et al. (1995) suggest, only medium and severe hypospadias represent deviations from a dimorphic ideal, then the incidence calculated from cases of hypospadias would be 0.5797/1,000, or 0.05%.

Several studies suggest that the rate of hypospadias has increased significantly in

the past two decades (Paulozzi et al., 1997; Toppari et al., 1996; Kristensen et al., 1997). Furthermore, severe hypospadias seems to have increased at a more rapid rate than the mild form, and there are both regional (within the U.S.) and national differences in overall rates of hypospadias, as well as in the rate of increase. While the cause of such increases is currently unknown, such trends mean that current estimates of the rate of intersexual births may require revision with time.

DISCUSSION

Adding the estimates of all known causes of nondimorphic sexual development suggests that approximately 1.7% of all live births do not conform to a Platonic ideal of absolute sex chromosome, gonadal, genital, and hormonal dimorphism. The incidence of hypospadias (0.05%) and cryptorchidism (0.4%), conditions of mixed origin affecting the apparently male population, are lower than the present estimate. However, the calculation includes categories which result in neither hypospadias nor cryptorchidism. The single largest contribution to the higher figure comes from late-onset CAH. If this cause of nondimorphism is deleted, the frequency estimates obtained from population surveys would come to 0.228%, the same order of magnitude found after combining the incidences of severe and medium hypospadias and cryptorchism (0.05 + 0.4 = 0.45%). Alternatively, if mild hypospadias and late-onset CAH in the final calculations are included the combined figure is 2.27% for hypospadias and cryptorchidism, compared with 1.728% obtained from summing the incidence of all known causes for which available data exist. These data, obtained using independent methods, are in general agreement. Which number one chooses to use depends on the specific population under study, and the assumptions as to what should count as true dimorphism. It would appear, however, that earlier estimates that intersexual births might run as high as 4% are unwarranted, except in populations in which a particular genetic condition occurs with high frequency (Fausto-Sterling, 1993a,b; Money, 1993).

Recently, a nascent social movement to recognize intersexuality as a legitimate state of nature has criticized medical approaches to the management of intersexuality (Nevada and Chase, 1995; Kessler, 1998) and these criticisms have begun to appear in more traditional medical settings (Diamond and Sigmundsen, 1997; Phornphutkul et al., 1999). Members of the Intersex Society of North America oppose the use of genital surgery to "normalize" children who are too young to decide for themselves whether to modify their genital structures. We define the intersexual as an individual who deviates from the Platonic ideal of physical dimorphism at the chromosomal, genital, gonadal, or hormonal levels. Not all intersexuals would be candidates for genital surgery. Lilford and Dear (1987) suggest that 0.05% (1 in 2,000) newborns have some ambiguity of the external genitalia, although they cite no medical or scientific literature to back up their claim. As one might expect, even given the data in Table 8, estimating the number of children subject to controversial genital surgery is an uncertain business. Turner and Klinefelter syndromes do not usually call for surgical intervention. However, many, although probably not all, of the other chromosomal alterations do, since they often result in intermediate genital development (Mittwoch, 1992). All of the hormonal disruptions potentially cause conditions which have been treated surgically. The highest frequency of intersexuality comes from late-onset CAH. When late-onset CAH occurs in childhood or adolescence and causes significant clitoral growth, it is quite possible that surgical intervention will ensue (Moreno and Goodwin, 1998). However, there is no way to estimate what proportion of late-onset CAH patients fall into this subcategory. Combining chromosomal deviations other than Turner or Klinefelter, all hormonal alterations, vaginal agenesis, true hermaphrodites, and idiopathic genital intersex, produces an estimate that 1.62% of the population may be subject to genital surgery as a treatment for intersexuality. Without late-onset CAH in this calculation, the estimate falls to 0.08%, or between one and two in a thousand. The true frequency of such surgeries probably lies somewhere in between.

Our culture acknowledges the wide variety of body shapes and sizes characteristic of males and females. Most sexual dimorphisms involve quantitative traits, such as height, build, and voice timbre, for which considerable overlap exists between males and females. Many cultures use dress code, hair style, and cultural conventions, e.g.,

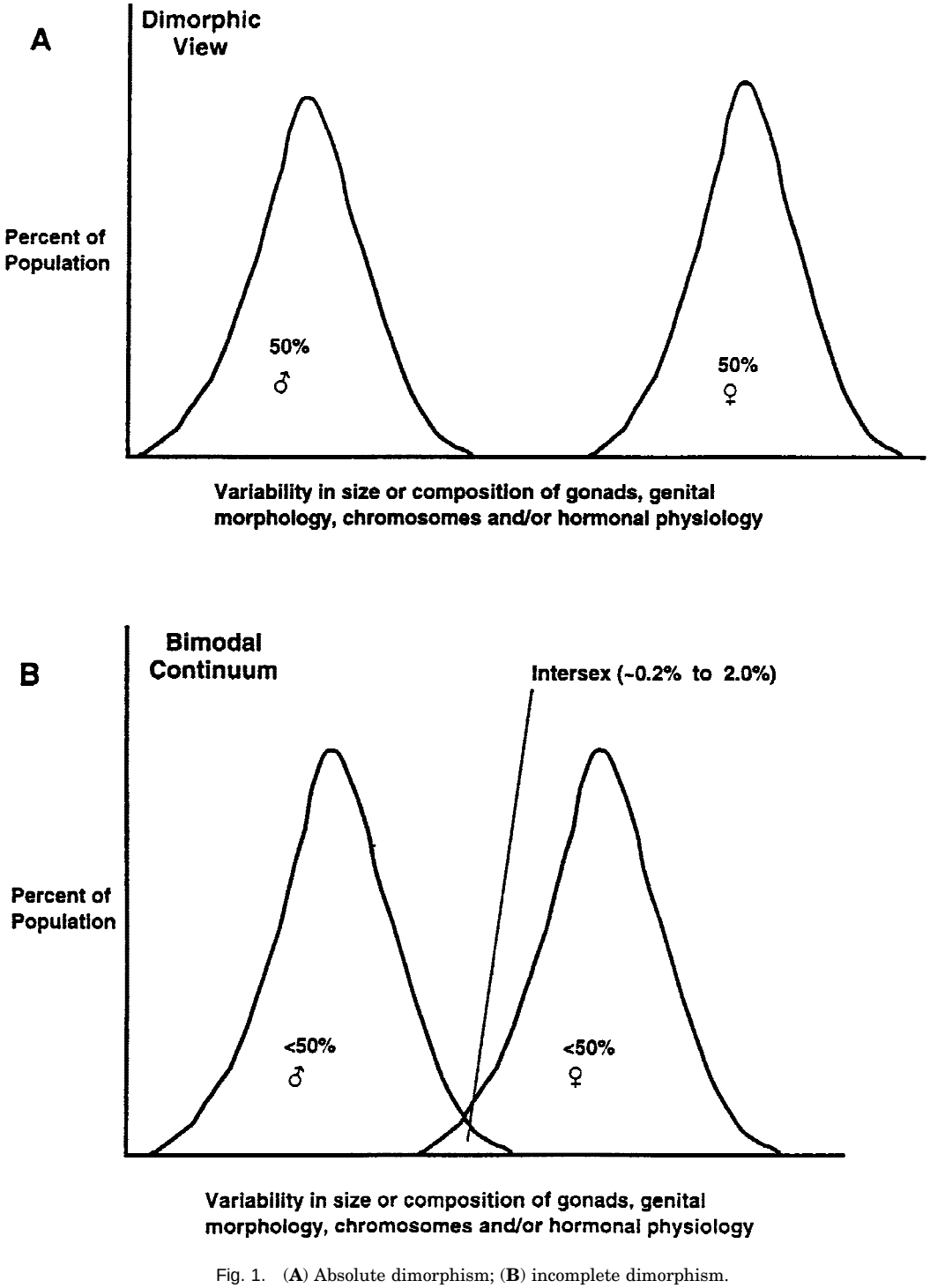

Fig. 1. (**A**) Absolute dimorphism; (**B**) incomplete dimorphism.

the view that in couples the male should be taller than the female, to accentuate awareness of such difference (see Unger and Crawford, 1992). But most consider that at the level of chromosomes, hormones, and genitals, dimorphism is absolute and, by implication, such traits are discrete rather than quantitative. Clearly, as a generalization, such a viewpoint makes some sense. However, developmental biology suggests that a belief in absolute sexual dimorphism is wrong. Instead, two overlapping bell-shaped curves can be used to conceptualize sexual variation across the population (Fig. 1). Within each major bell, genital morphology varies quantitatively, as shown, for example, by Fichtner et al. (1995). In the region of overlap, qualitative variation in chromosomal and genital morphology and in hormonal activity exists. If the view of the human population schematically illustrated in Figure 1B is accepted, the requirement for medical intervention in cases of intersexuality needs to be carefully reexamined. It seems likely that changing cultural norms concerning sex roles and gender-related behaviors may encourage a willingness to engage in such a reexamination.

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LITERATURE CITED

Aaronson IA, Murat CA, Key LL. 1997. Defects of the testosterone biosynthetic pathway in boys with hypospadias. J Urol 157:1884–1888.

Aarskog D. 1971. Intersex conditions masquerading as simple hypospadias. Birth Defects Orig Artic Ser 7: 122–129.

Abdullah MA, Katugampola M, Al-Habib S, Al-Jurayyan N, Al-Sammarrai A, Al-Nuaim A, Patel PJ, Niazi M. 1991. Ambiguous genitalia: medical, sociocultural and religious factors affecting management in Saudi Arabia. Ann Trop Paediatr 11:343–348.

Abramsky L, Chapple J. 1997. 47,XXY (Klinefelter syndrome) and 47,XYY: estimated rates of and indication for postnatal diagnosis for prenatal counseling. Prenat Diagn 17:363–368.

Aiman J, Griffin JE. 1982. The frequency of androgen receptor deficiency in infertile men. J Clin Endocrinol Metab 54:725–732.

Al-Attia HM. 1996. Gender identity and role in a pedigree of Arabs with intersex due to 5-alpha reductase-2 deficiency. Psychoneuroendocrinology 21:651–657.

Arnaut MA. 1992. Late onset congenital adrenal hyperplasia in women with hirsutism. Eur J Clin Invest 22:651–658.

Avellan L. 1975. The incidence of hypospadias in Sweden. Scand J Plast Reconstr Surg 9:129–139.

Bangsbøll S, Qvist I, Lebech PE, Lewinsky M. 1992. Testicular feminization syndrome and associated gonadal tumors in Denmark. Acta Obstet Gynecol Scand 71:63–66.

Bansal RK, Singh J. 1990. Congenital absence of the penis. Indian Pediat 27:882–884.

Bell AG, PN Corey. 1974. A sex chromatin and Y body survey of Toronto newborns. Can J Genet Cytol 16: 239–250.

Bochkov NP, Chebotarev AN, Alekhin VI, Midian SA. 1974. Population cytogenetic investigation of newborns in Moscow. Humangenetik 22:139–152.

Bois E, Mornet E, Chompret A, Feingold J, Hochez J, Goulet V. 1985. L'hyperplasie congenitale des surrenales (21-0H) en France (21-OH congenital adrenal hyperplasia in France). Arch French Pediatr 42:175–179.

Bryan A, Nigro J, Counseller V. 1949. 100 cases of congenital absence of the vagina. J Surg Gynecol Obstet 88:79–86.

Buckton KE. 1983. Incidence and some consequences of X-chromosome abnormalities in liveborn infants: cytogenetics of the mammalian X Chromosome. Part B: X chromosome abnormalities and their clinical manifestations. New York: Alan R. Liss. p 7–22.

Buckton KE, O'Riordan ML, Ratcliffe S, Slight J, Mitchell M, McBeath S, Keay AJ, Barr D, Short M. 1980. A G-band study of chromosomes in liveborn infants. Ann Hum Genet 43:227–239.

Burstein R, Wasserman HC. 1974. The effect of provera on the fetus. Obstet Gynecol 23:931–934.

Calzolari E, Contiero RM, Roncarati E, Mattiuz PL, Volpato S. 1986. Aetiological factors in hypospadias. J Med Genet 23:333–337.

Chervenak FA, Stangel JJ, Nemec M, Amin HK. 1982. Mayer-Rokitansky-Kuster-Hauser syndrome: congenital absence of vagina. NY State J Med 82:23–26 (Jan.).

Chung CS, Myrianthopoulos NC. 1968. Racial and prenatal factors in major congenital malformation. Am J Hum Genet 20:44–60.

Conte FA, Grumbach MM. 1989. Pathogenesis, classification, diagnosis and treatment of anomalies of sex. In: de Groot L, editor. Endocrinology. New York: Saunders. p 1810–1847.

Coran AG, Polley TZ Jr. 1991. Surgical management of ambiguous genitalia in the infant and child. J Pediatr Surg 26:812–820.

Currarino G. 1986. Large prostatic utricles and related structures, urogenital sinus and other forms of urethrovaginal confluence. J Urol 136:1270–1279.

Currie JL. 1974. Asymptomatic Mullerian anomalies. Med Ann DC 43:18–21.

Cutfield WS, Webster D. 1995. Newborn screening for congenital adrenal hyperplasia in New Zealand. J Pediat 126:118–121.

Danso AP, Nkrumah FK. 1992. The challenges of ambiguous genitalia. Cent Afr J Med 38:367–371.

Diamond, M. 1996. Prenatal predisposition and the clinical management of some pediatric conditions. J Sex Marital Ther 22:139–147.

Diamond M, Sigmundsen K. 1997. Management of intersexuality: guidelines for dealing with persons with ambiguous genitalia. Arch Pediatr Adolesc Med 151: 1046–1050.

Eldar-Geva T, Hurwitz A, Vecsei P, Palti Z, Milwidsky A, Rösler A. 1990. Secondary biosynthetic defects in

women with late-onset congenital adrenal hyperplasia. N Engl J Med 323:855–863.
Engstad JE. 1917. Artificial vagina. Lancet 15:336.
Fausto-Sterling A. 1993a. The five sexes: why male and female are not enough. Sciences March/April:20–24.
Fausto-Sterling A. 1993b. Reply. Sciences June/July:4.
Fausto-Sterling A. 1995/1996. Time to re-examine old treatment paradigms. Hermaphrodites with Attitude Fall/Winter:3.
Fedigan LM. 1982. Primate paradigms: sex roles and social bonds. Montreal: Eden Press.
Fichtner J, Filipas D, Mottrie AM, Voges GE, Hohenfellner R. 1995. Analysis of meatal location in 500 men: wide variation questions need for meatal advancement in all pediatric anterior hypospadias cases. J Urol 154:833–834.
Flatau E, Josefsberg Z, Reisner SH, Bialik O, Laron Z. 1975. Penile size in the newborn infant. J Pediatr 87:663–664.
Gearhart JP, Donohoue PA, Brown TR, Walsh PC, Berkovitz GD. 1990. Endocrine evaluation of adults with mild hypospadias. J Urol 144:274–277.
Gerald PS, Walzer S. 1970. Chromosome studies of normal newborn infants. In: Jacobs PA, Price WH, Law P, editors. Human population genetics. Edinburgh: Edinburgh University Press. p 144–151.
Gill B, Kogan S. 1997. Cryptorchidism: current concepts. Pediatr Urol 44:1211–1227.
Gill B, Kogan S, Starr S, Reda E, Levitt S. 1989. Significance of epididymal and ductal anomalies associated with testicular maldescent. J Urol 142:556–558.
Goad WB, Robinson A, Puck TT. 1976. Incidence of aneuploidy in a human population. Am J Hum Genet 28:62–68.
Golob E, Wagenbichler P. 1973. Geschlechtschromatin und fluoeszenzkorperchen von 1000 Neugeborenen. Geburts Frauenheilk 33:86–92.
Greenfield SP, Sadler BT, Wan J. 1994. Two-stage repair for severe hypospadias. J Urol 152:498–501.
Griffin JE, Wilson JD. 1989. The androgen resistance syndromes: 5-alpha reductase deficiency, testicular feminization and related disorders. In: Scriver CR, Beaudet AL, Sly WS, Valle D, editors. The metabolic basis of inherited disease. New York: McGraw Hill. p 1919–1975.
Hamerton JL, Canning N, Smith RM. 1975. A cytogenetic survey of 14,069 newborn infants. Clin Genet 8:223–243.
Hansteen I-L, Varslot K, Steen-Johnsen J, Langard S. 1982. Cytogenetic screening of a new-born population. Clin Genet 21:309–314.
Harkins JL, Gysler M, Cowell CA. 1981. Anatomical amenorrhea: the problems of congenital vaginal agenesis and its surgical correction. Pediatr Clin N Am 28:345–354.
Harlap S, Davis AM. 1973. Epidemiology of hypospadias. Br Med J 4(5886):235.
Harris LE, Steinberg AG. 1954. Abnormalities observed during the first six days of life in 8716 live-born infants. Pediatrics 14:314–326.
Hensleigh PA, Woodruff DA. 1978. Differential maternal-fetal response to androgenizing luteoma or hyperreactio luteinalis. Obstet Gynecol Surv 33:262–271.
Higurasi M, Iijima K, Ishikawa N, Hoshina H, Watanabe N. 1979. Incidence of major chromosome aberrations in 12,319 newborn infants in Tokyo. Hum Genet 46:163–172.
Hook EB, Warburton D. 1983. The distribution of chromosomal genotypes associated with Turner syndrome: live birth prevalence rates and evidence for diminished fetal mortality and severity in genotypes associated with structural X abnormalities or mosaicism. Hum Genet 64:24–27.
Ireland K, Woodruff JD. 1976. Masculinizing ovarian tumors. Obstet Gynecol Surv 31:83–111.
Ishizuka N, Kawashima Y, Nakanishi T. 1962. Statistical observations on genital anomalies of newborns following the administration of progestins to their mothers. J Japan Obstet Gynecol Soc 9:271–282.
Jacobson B. 1962. Hazards of norethindrone therapy during pregnancy. Am J Obstet Gynecol 84:962–968.
Jagiello G, Atwell JD. 1962. Prevalence of testicular feminisation. Lancet 1:329.
Jones HWJ, Wilkins L. 1967. Gynecological operations in 94 patients with intersexuality. Am J Obstet Gynecol 82:1142–1153.
Kallen B, Winberg J. 1973. The Swedish register of congenital malformations 1965–1971. Stockholm: Swedish Board of Health and Welfare.
Kallen B, Bertollini R, Castilla E, Czeizel A, Knudsen LB, Martinez-Frias ML, Mastroiacovo P, Mutchinick O. 1986. A joint international study on the epidemiology of hypospadias. Acta Paediatr Scand (Suppl) 324:5–52.
Kessler S. 1998. Lessons from the intersexed. New Brunswick, NJ: Rutgers University Press.
Kleczkowska A, Jean-Pierre F, Van den Berghe H. 1988. X-chromosome polysomy in the male. Hum Genet 80:16–22.
Kristensen P, Irgens LM, Andersen A, Bye AS, Sundheim L. 1997. Birth defects among offspring of Norwegian farmers 1967–1991. Epidemiology 8:537–544.
Krob G, Braun A, Kuhnle U. 1994. True hermaphroditism: geographical distribution, clinical findings, chromosomes and gonadal histories. Eur J Pediatr 153:2–10.
Kuhnle U, Schwarz HP, Löhrs U, Stengel-Ruthkowski S, Cleve H, Braun A. 1993. Familial true hermaphroditism: paternal and maternal transmission of true hermaphroditism (46,XX) and XX maleness in the absence of Y-chromosomal sequences. Hum Genet 92: 571–576.
Kumar H, Kiefer JH, Rosenthal IE, Clark SS. 1974. Clitoroplasty: experience during a 19-year period. J Urol 111:81–84.
Kumar A, Wakhlu AK, Chandra H. 1986. Congenital absence of the penis. Indian Pediatr 23:303–304.
Laue L, Rennert OM. 1995. Congenital adrenal hyperplasia: molecular genetics and alternative approaches to treatment. Adv Pediatr 42:113–143.
Lilford RJ, Dear PRF. 1987. The intersex baby. Br J Hosp Med 37:28–34.
Lin CC, Gedeon MM, Griffith P, Smink WK, Newton DR, Wilkie L, Sewall LM. 1976. Chromosome analysis on 930 consecutive newborn children using quinacrine fluorescent banding technique. Hum Genet 31: 315–328.
Lobe TE, Woodall DL, Richards GE, Cavallo A, Meyer WJ. 1987. The complications of surgery for intersex: changing patterns over two decades. J Pediatr Surg 22:651–652.
López M, Torres L, Mendez JP, Cervantes A, Pérez-Palacios G, Erickson RP, Alfaro G, Kofman-Alfaro S. 1995. Clinical traits and molecular findings in 46,XX males. Clin Genet 48:29–34.
Lorge F, Wese FX, Sluysmans T, Hennebert PN, Malvaux P, Maes M, Claus D, Capuyt P, Opsomer RJ, Van Cangh PJ. 1989. L'ambiguïté sexuelle: aspects urologiques. Acta Urol Belg 57:1989.
Lubani MM, Issa A-RA, Al-Saleh QA, Dudin KI, Reavey PC, El-Khalifa MY, Manandhar DS, Abdul-Al YK, Ismail EA, Teebi AS. 1990. Prevalence of congenital

adrenal hyperplasia in Kuwait. Eur J Pediatr 149: 391–392.
Lubs HA, Ruddle, FH. 1970. Chromosomal abnormalities in the human population: estimation of rates based on New Haven newborn study. Science 169: 495–497.
Maclean N, Harnden DG, Court Brown WM, Bond J, Mantle DJ. 1964. Sex-chromosome abnormalities in newborn babies. Lancet 1:286–290.
Mendoca BB, Inacio M, Costa EMF, Arnhold IJP, Silva FAQ, Nicolau W, Bloise W, Russell DW, Wilson JD. 1996. Male pseudohermaphroditism due to steroid 5α-reductase 2 deficiency. Medicine 75:64–75.
Mikamo K. 1968. Sex chromosomal anomalies in newborn infants. Obstet Gynecol 32:688–699.
Mittwoch U. 1992. Sex determination and sex reversal: genotype, phenotype dogma and semantics. Hum Genet 89:467–479.
Money J. 1993. Letter to the editor. Sciences June/July:4.
Moore KL. 1959. Sex reversal in newborn babies. Lancet 1:217–219.
Moreno A, Goodwin J. 1998. Am I a woman or a man? Mademoiselle March:178–181, 208.
Murken J, Stengel-Rukowsky. 1984. Klinefelter syndrome in prenatal diagnosis: incidence and consequences for genetic counseling. In: Bandmann HJ, Breit R, editors. Klinefelter syndrome. Berlin: Springer-Verlag. p 25–28.
Neto RM, Castilla EE, Paz JE. 1981. Hypospadias: an epidemiological study in Latin America. Am J Med Genet 10:5–19.
Nevada E, Chase C. 1995. Natural allies. Hermaphrodites with Attitude Summer:1–ff11.
New MI, White PC, Pang S, DuPont B, Speiser PW. 1989. The adrenal hyperplasias. In: Scriver C et al., editors. The metabolic basis of inherited disease. New York: McGraw-Hill. p 1881–1917.
Newfield RS, New MI. 1997. 21-Hydroxylase deficiency. Ann NY Acad Sci 816:219–229.
Newman K, Randolph J, Anderson K. 1992. The surgical management of infants and children with ambiguous genitalia. Ann Surg 215:644–653.
Nielsen J, Mogens W. 1991. Chromosome abnormalities found among 34910 newborn children: results from a 13 year incidence study in Arhus, Denmark. Hum Genet 87:81–83.
Oberfield SE, Mondok A, Shahrivar F, Klein JE, Levine LS. 1989. Clitoral size in full-term infants. Am J Perinat 6:453–454.
Oesterling JE, Gearhart JP, Jeffs RD. 1987. A unified approach to early reconstructive surgery of the child with ambiguous genitalia. J Urol 138:1079–1084.
Pang S, Clark A. 1990. Newborn screening, prenatal diagnosis, and prenatal treatment of congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Trends Endocrinol Metab 1:300–307.
Pang S, Clark A. 1993. Congenital adrenal hyperplasia due to 21-hydroxylase deficiency: newborn screening and its relationship to the diagnosis and treatment of the disorder. Screening 2:105–139.
Pang S, Murphey W, Levine LS, Spence DA, Leon A, LaFranchi S, Surve AS, New MI. 1982. A pilot newborn screening program for congenital adrenal hyperplasia in Alaska. J Clin Endocrinol Metab 55:413–420.
Pang S, Wallace MA, Hofman L, Thuline HC, Dorche C, Lyon ICT, Dobbins RH, Kling S, Fujieda K, Suwa S. 1988. Worldwide experience in newborn screening for classical congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Pediatrics 81:866–874.
Paulozzi LJ, Erickson JD, Jackson RJ. 1997. Hypospadias trends in two US surveillance systems. Pediatrics 100:831–834.
Paulsen CA, De Souza A, Yoshizumi T, Lewis BM. 1964. Results of a buccal smear survey in noninstitutionalized adult males. J Clin Endocrinol 24:1182–1187.
Pettersson F, Smedby B. 1973. In-patient statistics from hospitals in the Uppsala region 1964-1968. New born infants. Stockholm: Swedish Board of Health and Welfare, Reports, 12:1–21.
Phornphutkul C, Fausto-Sterling A, Gruppuso P. Gender self-reassignment in an XY adolescent male born with ambiguous genitalia. Pediatrics (in press).
Pinter A, Koxatolanyi G. 1990. Surgical management of neonates and children with ambiguous genitalia. Acta Paediatr Hung 30:111–121.
Pollack MS, Levine LS, O'Neill GJ, Pang S, Lorenzen F, Kohn B, Rondanini GF, Chiumello G, New MI, Dupont B. 1981. HLA linkage and B14,DR1,BfS haplotype association with the genes for late onset and cryptic 21-hydroxylase deficiency. Am J Hum Genet 33:540–550.
Post L. 1995/1996. Physicians: intersexual adults have much to teach you. Hermaphrodites with Attitude Winter:6.
Rajfer J, Walsh PC. 1976. The incidence of intersexuality in patients with hypospadias and cryptorchidism. J Urol 116:769–770.
Ramani P, Yeung CK, Habeebu SSM. 1993. Testicular intratubular germ cell neoplasia in children and adolescents with intersex. Am J Surg Pathol 17:1124–1133.
Raman-Wilms L, Tseng AL-i, Wighardt S, Einarson TR, Koren G. 1995. Fetal genital effects of first-trimester sex hormone exposure: a meta-analysis. Obstet Gynecol 85:141–149.
Ramsay M, Bernstein R, Zwane E, Page DC, Jenkins T. 1988. XX true hermaphroditism in Southern African Blacks: an enigma of primary sexual differentiation. Am J Hum Genet 43:4–13.
Ratcliffe SG, Axworthy D, Ginsborg A. 1979. The Edinburgh study of growth and development in children with sex chromosome abnormalities. Birth Defects Orig Artic Ser 15:243–260.
Roberts CJ, Lowe CR, Lloyd S. 1972. Cyclic variations in date of last menstrual period of mothers of infants with congenital malformations in South Wales, 1964–1966. Br J Prevent Soc Med 26:212–218.
Rösler A, Esther L, Cohen T. 1992. High frequency of congenital adrenal hyperplasia (classic 11-beta hydroxylase deficiency) among Jews from Morocco. Am J Med Genet 42:827–834.
Rupprecht T, Deeg KH, Bohles HJ. 1989. Penisagenesie. Klin Padiatr 201:409–411.
Sack J, Front H, Kaiserman I, Schreiber M. 1997. 21-Hydroxylase deficiency: screening and incidence in Israel. Horm Res 48:115–119.
Sandberg D. 1995/1996. A call for clinical research. Hermaphrodites with Attitude Winter:8–9.
Schreinemacher DM, Cross PK, Hook EB. 1982. Rates of trisomies 21, 18, 13 and other chromosome abnormalities in about 20,000 prenatal studies compared with estimated rates in live births. Hum Genet 61: 318–324.
Scorer CG, Farrington GH. 1971. Congenital deformities of the testis and epididymis. New York: Appleton-Century-Crofts.
Sergovich F, Valentine GH, Chen ATL, Kinch RAH, Smout MS. 1969. Chromosome aberrations in 2159

consecutive newborn babies. N Engl J Med 280:851–855.
Shapiro RN, Eddy W, Fitzgibbon J, O'Brien G. 1958. The incidence of congenital anomalies discovered in the neonatal period. Am J Surg 96:396–400.
Skordis NA, Stetka DG, MacGillivray MH, Greenfield SP. 1987. Familial 46,XX males coexisting with familial 46,XX hermaphrodites in same pedigree. J Pediatr 110:244–248.
Slaney SF, Chalmers IJ, Affara, NA Chitty, LS. 1998. An autosomal or X-linked mutation results in true hermaphrodites and 46,XX males in the same family. J Med Genet 35:17–22.
Smithells RW. 1968. Incidence of congenital abnormalities, 1960-1964. Br J Prevent Soc Med 22:36–37.
Sólyom J, Hughes IA. 1989. Value of selective screening for congenital adrenal hyperplasia in Hungary. Arch Dis Child 64:338–342.
Speiser PW, Dupont B, Rubinstein P, Piazza A, Kastelan A, New MI. 1985. High frequency of nonclassical steroid 21-hydroxylase deficiency. Am J Hum Genet 37:650–667.
Steinberger E, Odell WD. 1989. Genetics, anatomy and fetal endocrinology. In: de Groot L, editor. Endocrinology. 2nd ed. New York: Saunders. p 1801–1809
Stevenson AC, Johnston HA, Stewart MIP, Golding DR. 1966. Congenital malformations: a report of a study of series of consecutive births in 24 centres. Bull WHO (Suppl) 34:66–69.
Stoll C, Alembik Y, Roth MP, Dott B. 1990. Genetic and environmental factors in hypospadias. J Med Genet 27:559–563.
Subray NN, Prabhaker SN. 1962. Sex chromatin anomalies in newborn babies in India. Science 136: 1116.
Sweet RA, Schrott HG, Kurland R, Culp DS. 1974. Study of the incidence of hypospadias in Rochester, Minnesota, 1950–1970, and a case-control comparison of possible etiologic factors. Mayo Clin Proc 49:52–59.
Therrell BL, Berenbaum SA, Manter-Kapanke V, Simmank J, Korman K, Prentice L, Gonzalez J, Gunn S. 1998. Results of screening 1.9 million Texas newborns for 21-hydroxylase-deficient congenital adrenal hyperplasia. Pediatrics 101:583–590.
Thilén A, Larsson A. 1990. Congenital adrenal hyperplasia in Sweden, 1969-1986. Acta Paediatr Scand 79: 168–175.
Thompson R, Seargeant L, Winter JSD. 1989. Screening for congenital adrenal hyperplasia: distribution of 17alpha hydroxyprogesterone concentrations in neonatal blood spot specimens. J Pediatr 114:400–404.
Toppari J, Larsen JC, Christiansen P, Giwercman A, Grandjean P, Guilette LJ, Jegou B, Jensen TK, Jouannet P, Keiding N, Leffers H, McLachlan JA, Meyer O, Müller J, Rajpert-DeMeyts E, Scheike T, Sharpe R, Sumpter J, Skakkebaek NE. 1996. Male reproductive health and environmental estrogens. Environ Health Perspect 104(Suppl 4):741–803.
Trichopoulos D, Cadas C, Kalapothaki V, Pimenidou E. 1973. Epidemiology of hypospadias. Br Med J 4:109.
Unger R, Crawford M. 1992. Women and gender: a feminist psychology. New York: McGraw Hill.
Verhoeven ATM, Mastboom JL, Van Leusden HAIM, Van der Velden WHM. 1973. Virilization in pregnancy coexisting with an (ovarian) mucinous cystadenoma: a case report and review of virilizing ovarian tumors in pregnancy. Obstet Gynecol Surv 28:597–622.
Verma IC, Bawa B, Chai OP, Guaha DK. 1973. Survey of X chromatin aberrations in newborn babies in Delhi. Indian Pediatr 10:537.
Vogel F, Motulsky AG. 1979. Human genetics: problems and approaches. Berlin: Springer-Verlag.
Walcutt H. 1995/1996. Physically screwed by cultural myth: the story of a Buffalo Children's Hospital survivor. Hermaphrodites with Attitude Winter:10–13.
Walzer S, Park G. 1977. A chromosome survey of 13751 male newborns. In: Hook EB, Porter IH, editors. Population cytogenetics: studies in humans. New York: Academic Press. p 45.
Werder EA, Siebenmann RE, Knorr-Murset G, Zimmermann A, Sizonenko PC, Theintz P, Girard J, Zachmann M, Prader A. 1980. The incidence of congenital adrenal hyperplasia in Switzerland—a survey of patients born in 1960–1974. Helv Paediatr Acta 35:5–11.
White PC, New MI, DuPont B. 1987. Congenital adrenal hyperplasia. N Engl J Med 316:1519–1524.
Wilkins L. 1960. Abnormalities of sex differentiation: classification, diagnosis, selection of gender of rearing and treatment. Pediatrics 26:846–857.
Wilkins L. 1965. Abnormal sex differentiation: hermaphroditism and gonadal dysgenesis. In: The diagnosis and treatment of endocrine disorders in childhood and adolescence. 3rd ed. Springfield, IL: Charles C. Thomas. p 297–338.
Willemsen WNP, Dony JMJ. 1988. Een decennium ervaring met de behandeling van hypo-en aplasie van de vagina met de neovaginaplastiek volgens Davydov en met de (niet-operatieve) method van Frank. Nederlandse Tijdschrift voor Geneeskunde 132:1199–1202.
Zinn AW, Page DC, Fisher EMC. 1993. Turner syndrome: the case of the missing sex chromosome. Trends Genet 9:90–93.
Zucker KJ. 1996. Commentary on Diamond's "Prenatal predisposition and the clinical management of some pediatric conditions." J Sex Marital Ther 22:148–160.